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EDITORIAL COMMENT

There are, in this issue, three non-scientific articles which may be of great interest to many students and graduates. "The Grenfell Medical Mission" by R. B. Salter is a colourful description of the author's experiences in Newfoundland and of the conditions prevailing there. Mr. Salter has adequately indicated that efficient medical services can be established in places where poor geographic and economic conditions exist.

S. R. Frankling relates some of his experiences as a laboratory technician in "A Medical Student's Experiences". He describes the advantages of a summer spent in this capacity.

In "Khaki College", H. P. Higgins writes about the university training made available to Canadian servicemen by the Canadian Army in England. He is one of the many Canadians who took advantage of this plan.

The policy of this Journal is to publish both articles of scientific and of general interest. Of the latter, those articles relating to student summer experiences are especially desirable. In this way many opportunities may be presented to your fellow students.

The success of this Journal is the responsibility of the undergraduate body as well as the Editorial Staff. Articles contributed by the former insure the Journal's useful publication. Manuscripts should be typed and double spaced. These may be given to Journal representatives or mailed to Room 107 Anatomy Building.

ERRATUM

Pulmonary Tuberculosis and the General Practitioner; Vol. XXIV, Number 2, P. 54, 2 (b). The cost per capita in the survey in Saskatchewan is 9 cents instead of 90 cents.

KHAKI COLLEGE

H. P. HIGGINS 5T0

The Khaki University of Canada in the United Kingdom, or as it was more commonly known, "Khaki College", was perhaps the most daring and the most successful experiment of the Canadian Army, in rehabilitation. It was designed primarily for those who had the educational qualifications to enter University, or had attended University for a year before they joined the army. It was felt by the authorities at home, that men and women in this category, who for the most part had just short of the point score required for return to Canada, should have an opportunity to continue their education.

This thought saved many a career. For, after the first flush of victory had worn off, the outlook of most of the younger troops was anything but bright. They foresaw a year or more of the most unpleasant aspects of army life, "guard duty and fatigues". Occupations that might well have removed all traces of ambition, all thirst for knowledge, from the minds of young men in the most critical years of their lives.

This problem was thrown, without ceremony, into the lap of Brigadier G. C. Beament, O.B.E., E.D., B.A.Sc. (M.E.) The foresight of the "Brig" as he was affectionately known to the students, in handling this problem, produced "Khaki College". Starting with but an idea, a keen knowledge of human nature and a determination that was to upset the plans of many brass hats (who felt that the more a soldier knew, the harder he was to control) he built and staffed "Khaki College" so that its facilities were second to none of the Canadian Universities, and in some respects far superior to all.

The courses offered included practically all those offered in the Universities at home for 1st and 2nd years (1st year U. of T.), and the student was able to choose subjects for which he would get credit in the faculty he wished to enter on return to Canada.

The time table was arranged so that a year's work in a maximum of three subjects could be completed in a three and a half months term, and there were two such terms. Thus, students who were repatriated at the end of the 1st term were able to complete a year's work in three subjects. Students who stayed for the two terms were able to complete a year's work in six subjects.

The staff was first rate, and included such men as Dr. Petrie of the University of New Brunswick, Dr. B. S. Rabinovitch of McGill University and Dr. Barnacotte of the University of London, England.

Due to the small numbers in each class, from ten to twenty, and at the most fifty, the professors were able to give individual attention and to contact the students to a far greater degree than is possible here. This led to a better and more thorough appreciation by the students of the subjects taught.

The authorities of the University of London (England) who served as advisers and examiners, and even supplied some professors, were pleased, and even astonished at the high quality of the work done by the students. Since the students were

Cultural activities of all sorts were offered by the situation of the University at the heart of England. Tours to Oxford, Cambridge, Wales and Dover, to beauty spots, historic sites, beautiful buildings and magnificent views were conducted by the Y.M.C.A. attached to the University. Opportunities to attend the best plays in London, to hear symphonies at Royal Albert Hall, and many other forms of activity were offered. But last, and certainly not least was the opportunity to talk to, to listen to, and to know the "Englishman" over a pint of beer in the local "pub".

In the future many names of those who look to K.U. of C. as their Alma Mater, will come into the limelight in Canada; but all who attended have profited in many ways and they will look back on their days at "Khaki" as some of the most enjoyable and stimulating of their lives.

LYMPHOGRANULOMA INGUINALE

J. C. PEARSON, 4T7

In medical literature Lymphogranuloma Inguinale has been called Lymphogranuloma Venereum, Climatic Bubo, Lymphopathia Venereum, Poradenitis, and Poradenolymphitis. This has resulted in much confusion regarding this disease. Of all these terms I think the name Lymphopathia Venereum is the most suitable since this signifies that it is a venereal lesion of the lymphatic system.

This disease may be defined as a specific infectious venereal disease affecting the lymph channels and nodes, characterized by a transient primary lesion, often undetected, followed by a subacute lymphadenitis with eventual suppuration, formation of fistulae and finally cicatricial healing.

Historical.

Cases of a similar nature have been described since 1533. However it was not until 1833 when William Wallace of Dublin described a case which he called "indolent primary Syphilitic Bubo" and gave several features in which it differed from Syphilis that an accurate case was recorded. Several cases of the disease were described in America in 1885. A great advancement was made late in the 19th century, when Klotz, a surgeon, became accidentally infected during an operation and from his observations he deduced the disease was neither Syphilis nor Tuberculosis. At this time it was generally believed that the disease was a form of Tuberculosis. Another great step forward resulted from the publication of a paper by Durand, Nicolas & Favre in 1913. They noted a sex incidence (commoner in the male); observed a herpetiform lesion on the genitalia of many of their cases; associated it as a venereal disease and theorized the aetiological agent as an unknown virus. It is due to these men that the unfortunate name of Lymphogranuloma Inguinale arose since to them the pathological examination showed a similarity to Hodgkin's disease and thus they concluded that it was a lymphadenoma. These men also noted the associated enlarged iliac glands found in Lymphogranuloma Inguinale. The third great advancement was made in 1925 by Frei who developed the intracutaneous test, known as the Frei Test, which is still used in the diagnosis of this disease. Since then, Hellerstrom has transmitted the infection to animals and numerous men have isolated the aetiological factor.

Aetiology

The causative agent is a filtrable virus of a magnitude between 0.125-0.175 microns. This has been cultured by several investigators using a chorioalantoic membrane as the medium. Thus far the virus has been obtained from the regional lymph nodes, urethral and vaginal discharges, pelvic abscesses, spinal fluid, blood stream, inflamed rectal tissue and the conjunctivae. In the case diagnosed at the Toronto Western Hospital in 1946, Dr. Labzoffsky of the Ontario Department of Health isolated the virus.

Predisposing factors include lack of cleanliness, a redundant prepuce and trauma to the genitalia.

INCIDENCE

While it is commoner in the male sex, it is not uncommon in the female. The theory that females may act as carriers in some cases has yet to be proven. Unlike Granuloma Inguinale, there is no marked racial disposition and the infection occurs in all races including the White. In the report of 750 males cases from the Panama, 36% of the cases occurred in white residents. Only 11% of the series were Negro residents while the majority of cases were transient visitors to the area. The infection is disseminated by sexual contact and hence the incidence is greatest where prostitution flourishes. A few cases have been reported from accidental causes.

While there is no selective geographical distribution, the infection is commonest in the warm climates.

Only 4 cases have been reported in Canada since 1933. However, as a result of the war, numerous cases are seen on both coasts. Dr. Baker of the Department of Venereal Disease Control, saw 10 cases in Halifax in one day. These were in troops returned from Italy. As yet, no estimate has been made by the Armed Services on the incidence in returned men.

In the Gorgas Hospital, Panama, in the 7-year period ending Sept., 1944, 6.1 per 1,000 male hospital admissions had Lymphogranuloma Inguinale.

PATHOLOGY

The gross pathological picture varies with the stage of the disease. Early the glands are discrete but later become matted together and attached to skin by fibrous tissue. They are of moderate firmness in consistence and the size varies from normal to moderately enlarged (size of a hen's egg). When suppuration occurs, the glands are soft and discharge to the surface through numerous fistulae.

The early microscopic appearance shows minute inflammatory foci scattered throughout the gland substance with numerous lymphocytes, plasma cells, eosinophiles and endothelial phagocytes present. Later, polymorphonuclears predominate with the formation of small abscesses. These are lined by epithelioid cells arranged in pallisade formation with a few giant cells present. The gland capsule is thickened and there are subcapsular hemorrhagic infiltrations and oedema of the peripheral sinuses. The picture is that seen in any chronic granuloma and hence the early mistaken relationship to Tuberculosis and Syphilis was made. However, true caseation and calcification are never found. Fistulous tracts may form, from which exudes clear sticky mucous fluid. When cultured, this fluid shows no organisms.

Finally, sclerosis of the gland tissue occurs. This is seen most commonly in the rectal area and is the factor resulting in elephantiasis in some cases. In 1938 Miyagama showed the presence of intracellular virus particles.

CLINICAL MANIFESTATIONS

The manifestations of this infection are bizarre. The incubation period varies from a few days to one week after coitus, when a primary lesion may be observed. However as the primary lesion is not commonly seen (in 4 out of 130 cases—Hanschell), the first observation is inguinal adenopathy occurring 10 days to 3 weeks after exposure.

The primary lesion may be one of 3 types:

(1) The commonest form is a fleeting herpetic lesion, vesicle or ulcer occurring anywhere on the genitalia. There is little surrounding induration and the lesion is painless, non pruritic, and generally heals spontaneously. This explains its non-recognition in many cases.
(2) A nodular lesion of varying size with central ulceration.
(3) An intra-urethral lesion of an ulcerative nature with a more or less circumscribed thickening in the course of the urethra, accompanied by a non-specific urethral discharge.

The similarity of the above types to the primary syphilitic lesion is quite obvious and explains one of the difficulties of diagnosis.

It is the contention of Hellerstrom and certain other writers that the adenopathy does not necessarily occur in all cases and may be minimal in other cases. However, it is generally believed that involvement of the lymph nodes occurs in most cases. This is called the Secondary Stage of Lymphogranuloma Inguinale and occurs one to three weeks after exposure. Generalized symptoms are present at this stage and may take the form of any infection. Fever, chills, lassitude, polyarthritis, headache, abdominal cramps, nausea and vomiting, pleuritic pain, and meningeal symptoms have all been reported. The fever may be of the remittent, intermittent or of the typhoid type.

The earliest symptom complained of may be some stiffness or aching in the groin. This is followed by swelling in that area. Examination at this time shows unilateral, less commonly bilateral, swelling of the inguinal lymph glands. Tucker reports only 20% of his 750 cases were bilateral. The gland swelling may undergo spontaneous retrogression or progress to suppuration. As periadenitis occurs, the overlying skin becomes fixed and has a characteristic bluish red appearance. Clinically, there is a large, oval, lobulated hard swelling in the groin.

The Tertiary Stage of Lymphogranuloma Inguinale is one of suppuration and fistulae formation. Characteristically, fluctuation of the inguinal mass occurs and with the ulceration of the overlying skin, numerous fistulae are formed and there is a purulent discharge. The percentage of cases reaching this stage has not yet been estimated. Gradual healing takes place in four to eighteen months with much scarring.

The route for the above infection is via the coronal sulcus of the penis through the penile lymphatics to the inguinal lymph glands. A further spread may occur to the deep iliac glands. Hellerstrom estimates that this occurs in 36% of cases. One very characteristic feature of the iliac adenopathy is that it almost never progresses to suppuration.

The history as cited above is typical of the infection as it occurs in the male. However in the female the picture is different due no doubt to the peculiarities of the lympathic drainage of the female genitalia. In brief, the lymph from the clitoris and external vulva drains into the inguinal glands while that from the vagina drains into three lymph plexuses situated about the lower part of the rectum. This is controversial but investigation has shown there is a definite relationship.

Thus, inguinal adenitis is relatively rare in the female while peri-rectal and deep pelvic involvement are relatively common.

As to the occurrence of generalized adenopathy, there is some controversy. However, animal experiments have shown that it can occur and thus, the best conclusion is that it can occur in humans but rarely does.

Perhaps the most important feature is the late manifestation of rectal stricture. This stage of the infection is also known as Esthiomene, Genito-Ano-Rectal Syndrome and Ano Rectal Syphiloma. Until recently, this was considered as a separate entity. However, the development of the Frei test and close observation showed this syndrome as a further stage of Lymphogranuloma Inguinale. Vander Meer in 1935 reported 47 cases of Lymphogranuloma Inguinale of which 21 had rectal strictures. All of these occurred in female patients. This sex incidence is explained on the basis of the area drained by the rectal lymph nodes as was pointed out previously. McLaughlin states that ano-rectal lesions do not occur in the male after normal coitus, no matter how severe the infection. Cole, who has made the most extensive study of this phase of the infection, explains the sequence of events as follows: "infection spreads to the rectal and pelvic lymph nodes with subsequent inflammation of the rectal wall; lymph thrombosis occurs and ulceration of the rectal mucosa usually also occurs. Subsequent healing results in the narrowing of the rectal lumen. The site of stricture is usually four to six cms. from the anus, and may be either band-like or tubular depending on the extent of rectal involvement. Elephantiasis of the labiae, vulva, perineum, or anus may result from the lymph stasis produced by the marked scarring. Physical examination shows ragged ulceration and cauliflower indurated lesions about the anal orifice. Digital examination reveals a firm inelastic contracture involving the whole circumference of the rectum. The signs and symptoms at this stage are bloody purulent anal discharge followed by difficulty in defecation.

DIAGNOSIS.

The diagnosis is made on the history, clinical picture and Frei's intradermal test. The history of a primary stage is often lacking and with a bizarre clinical picture, the diagnosis would be difficult were it not for the Intracutaneous Test. This consists of the injection of 0.1 cc. of antigen using normal saline as a control. The test should be read between the second and fifth day and a positive test is one in which there develops an inflammatory nodule or papule greater than 0.6 cms. in diameter, with or without central necrosis. In brief, the antigen is prepared from aspirated pus from an involved lymph node in a clinically diagnosed case. This is mixed with physiological saline and the mixture is heated to 60°C. for 90 mins. and on the succeeding day to 60°C. for 60 mins. Frei claims it to be 95% specific. More recently Lygranum, produced by Squibb Co., has been used for the test. The test is interfered with by high fever, tuberculosis and Syphilis. The test remains positive for life despite clinical cure of the disease. McLaughlin, in 40 cases diagnosed clinically, found only 62% had a postive Frei Test and states that not too much emphasis should be placed on the result. Stitt's figures show 80% of cases with rectal stricture have a positive test.

Other features in the diagnosis include a White Blood Count of approximately 8,500, increased blood cholesterol, increased serum globulin and decreased serum albumin. This reversal of the albumin-globulin ratio has been used by several investigators in the diagnosis of the disease. The so-called Formol Gel Test consists of adding patient's serum to formalin. A positive test is one in which there develops marked opacity and viscosity. False positives are obtained in Syphilis (20%) and Granuloma Inguinale (16%). In addition, the test is of value in determining the activity of the disease and the effect of treatment. A negative test is obtained in approximately 6 weeks after treatment with Sulphadiazine.

In approximately 10% of cases, skin manifestations are seen. These include erythema nodosum, erythema multiforme, urticaria and a scarlatiniform eruption. It is now accepted that these are allergic reactions and not a metastasis as claimed by Koppel. They are seen most commonly following treatment of the bubo by irradiation or after the intradermal skin test.

Differential Diagnosis.

(1) Syphilis. The lymph nodes are generally enlarged and remain sharply defined, hard, and painless. Examination of the primary lesion shows a positive dark field and later, the blood Wassermann becomes positive. However, occasionally patients with Lymphogranuloma Inguinale may give a +++ false positive Wassermann reaction. Finally, Syphilis may be acquired at the same time as the Lymphogranuloma Inguinale, thus giving a very bizarre clinical picture with confusing laboratory tests. Thus great care must be taken in diagnosing one or the other or a combination of these diseases.

(2) Chancroid. The distinguishing points are an acute painful adenitis with one central area of necrosis discharging through a single fistula. Examination of a stained smear from the lesion shows the Bacillus of Ducrey. In the later stages there is a specific intradermal bacillary test corresponding to the Tuberculin Test.

(3) Bubonic Plague. In this, the glands are exquisitely tender accompanied by marked constitutional symptoms. Aspirations of a bubo shows the organism to be Bacillus Pestis.

(4) Granuloma Inguinale. There should be little confusion between these two infections other than the similarity of the names. Granuloma Inguinale is a disease of the skin that spreads through the skin itself while Lymphogranuloma Inguinale is a disease primarily of the lymphatic system with secondary involvement of the overlying skin. Smears from the lesions of Granuloma Inguinale show the pathognomonic Donovan bodies.

Occasionally, there is difficulty differentiating Hodgkin's Disease, Tuberculosis and Malignant growth. A special point must be made regarding the rectal stricture. Curtis believes that all inflammatory strictures of the rectum, not due to trauma of hemorrhoidectomy, should be considered as Lymphogranuloma Inguinale.

TREATMENT.

The multiplicity of remedies as cited below indicates the inconclusive results of the various methods used. The primary lesion heals with any simple local applicant such as Zinc Oxide ointment and in most cases will heal spontaneously. When the general constitutional symptoms appear, the patient should remain in bed. If the buboes are painful, wet compresses and light mercurial ointments over the affected area often give relief. With the advent of the sulphonamides, investigators thought that they had a specific remedy. The reports so far indicate that sulphonamides have a definite value in early cases. McLaughlin treated 26 of his 50 cases with sulphonamides and found that 21 of them responded well. Stein treated 35 cases with good results. Tucker is a strong advocate of sulphonamide therapy for early cases. His patients receive Sulphathiazole *stat* 4 gms. and then 1 gm. *q* 4 *h.* until a minimum of 40 gms. has been given. Yater found sulphonamides only beneficial in reducing secondary infection. He bases this on the fact that sulphonamides are ineffective against viruses. Further investigation will be necessary before the final word is given. As yet, no papers have appeared on the use of the newer antibiotics.

Previously Tartar Emetic in 10 cc. doses was given intravenously for eight to thirty-two injections. Stannus obtained good results in 50% of 85 cases treated in this way. Other drugs used include antimony, arsenic, mercury, iodides, copper and gold. Frei and others have made vaccines from excised glandular tissue but with disappointing results. X-ray therapy has its advocates but it is generally found that more extensive scarring results.

Chronic cases are best treated by partial extirpation of the nodes. Tucker found that 31% of his 750 cases had to have surgical intervention. The objective was open drainage of the fluctuating lymph nodes. Contrary to most workers, he used radical excision in selected cases with few complications such as elephantiasis.

Rectal stricture requires separate treatment which consists of repeated dilatation. Advanced cases require colostomy and resection of the rectum.

CONCLUSIONS.

(1) Lymphogranuloma Inguinale is a venereal disease cause by a filtrable virus, that has a world-wide distribution.

(2) The disease has primary, secondary and tertiary stages, the first of which is seldom seen.

(3) Clinical manifestations appear with the secondary stage but are not characteristic. The site of the adenopathy varies with the sex.

(4) The diagnosis is made from the history, the Frei Intradermal Test, the Formal Gel Test and the physical examination.

(5) Treatment of early cases is best carried out with Sulphadiazine. Late cases require surgical drainage.

(6) Rectal Stricture is the advanced stage found in the female and requires repeated dilatation.

REFERENCES

Stannus, H. S.—A Sixth Venereal Disease.

Curtis—Textbook of Gynaecology.

Boyd, W.—Textbook of Pathology.

Cecil—Textbook of Medicine.

Yater—International Medicine.

Stitt—Tropical Diseasess.

McLaughlin—Lancet June/45 R.A.F. 50 cases.

Comles, Ganizares, Landy—American Journal of Syphilis, Gonorrhea, and Venereal Diseases Nov./45.

Tucker—Amer. J. of Syph., G., V.D. Nov./45.

Cole—J.A.M.A. 1933, 101, 1069.

Editorial—J.A.M.A. 1937, 109, 876.

Wien—J.A.M.A. 1937, 108, 27.

Napier—Tropical Diseases.

Cole and Jewel L.—C.M.A.J. Oct./46.—Case of Lymphogr. Inguinale at T.W.H.

INTESTINAL OBSTRUCTION—PART 1

W. WEISBROD 4T7

It is impossible to cover a field so vast as intestinal obstruction in a short paper. Consequently, this paper attempts to cover a limited sector of the topic, a sector which has been most controversial up to the present time. The physiological and mechanical principles underlying the treatment and the cause of death in intestinal obstruction will be discussed.

A. PHYSIOLOGICAL AND BIOCHEMICAL PRINCIPLES

I. Factors contributing to distention in obstruction.

(a) *Gases;* the possible sources of gases are from the digestive processes, the diffusion of blood gases into the intestinal lumen, and the passage of swallowed air into the intestine. During digestion, considerable carbon dioxide may form from the mixture of gastric hydrochloric acid with the alkaline biliary and pancreative secretions. A considerable amount of gas may also form from the action of bacteria on cellulose, carbohydrates or proteins. Carbon dioxide and oxygen are readily diffusible across the intestinal wall; nitrogen is absorbed very slowly.

Wangenstein and Rea investigated the swallowed air factor in 1939 by performing an oesophagostomy with subsequent terminal ileal obstruction. They concluded that 68% of gases in the intestine is swallowed air; the other 32% consisted of diffused blood gases and gases originating in the intestinal loop in the ratio of 7:3.

(b) *Fluids:* the source of fluids contributing to distention in obstruction consists of ingested fluids, either in fluid form or combined with water of crystallization, water form , colloid hydration or carbohydrate metabolism. The water is absorbed as a solution, the osmotic pressure of which is the same as that of the blood serum.

The normal inflow of secretions into the gasro-intestinal tract consists of 7-8.5 litres per day. This volume is made up of 1.5 litres of saliva, 2-3 litres of gastric juices, 300-500 ccs. of bile, 500-800 ccs. of pancreatic juice and 3 litres of intestinal juice. There is strong evidence that the alimentary fluids may be considerably increased in distention.

The degree to which fluid secretions contribute to distention depends on the location and degree of the obstruction. In high small bowel obstructions the intestinal fluids are readily vomited. In low small bowel obstructions the vomiting of fluid may be just as great, but the accumulation of fluid and the associated distension will be greater than in high obstruction. In colonic obstruction loss of fluid through vomiting is negligible.

II. Manifestations of distention on the bowel wall.

There are essentially two varieties of obstruction (a) simple obstruction, in which continuity of the bowel alone is interrupted, and (b) strangulating obstruction in which there is also impaired blood supply. Distention may simulate, in part, some effects of strangulating obstructions.

(1) *Influence of the site of obstruction upon the effects of distention.*

(a) In complete simple obstruction of the duodenum, distal to the pancreatic and bile entrance, death occurs in 3-4 days with oligurea leading to anurea, nitrogen retention, hypochloremia and alkalosis. In low ileal obstructions, vomiting does not empty the lower small intestines; the fluid present thereby contributes to distention. In colonic obstructions the contents of small bowel are permitted free entry to the colon; because of the ileo-cecal valve and sphincter, regurgitation into the terminal ileum occurs infrequently. Harper and Lemmer (1945) working on experimental obstruction in animals, concluded that the lower the obstruction, the greater the incidence and degree of haemorrhage, necrosis and ulceration of the intestinal wall. Bacteria acting upon tissue whose resistance is lowered by ischemia due to distention are responsible for ulceration. The lower the obstruction, the greater the degree of distention, the greater the kinking and the formation of isolated loops, the greater the percentage of positive peritoneal cultures at autopsy.

(2) *The effects of distention.*

The main effect of distention is on the bowel wall.

(a) *Effect on the physical characteristics of the bowel wall.*

Sperling found shortening of bowel wall by 20-33% in acute obstruction. As the bowel distends, contraction of the longitudinal muscle results in shortening. In chronic obstruction, lengthening is not unusual.

In terminal ileal obstruction, the empty segments become heavier toward the site of the obstruction. When allowance is made for shortening of the bowel, there is a 34% increase in weight in acute obstruction.

Sperling and Wangenstien found the bursting strength of the ileum and jejunum lay between 140-260 mm. Hg., while that of the colon was 80 mm. Hg. The bursting strength of an obstructed segment of small bowel is reduced to 50% of normal.

(b) *Intra-enteric pressure in bowel obstruction.*

In small bowel obstruction Morton and Sullivan found pressures in jejunal loops of 52 cms. H_2O, while ileal pressure was 8 cms. H_2O. They attribute the difference to the greater secretion in the jejeunal loops.

In obstruction colon, pressures were higher than in obstructed ielum, varying between 12-52 cms. H_2O. The ileo-cecal valve and sphincter may convert a simple colonic obstruction into a closed loop obstruction. Because of this, unrelieved colonic obstruction may result in perforation of the cecum.

(c) *Effects on the contractility of the bowel.*

Brandberg noted an initial increase in contractility; with increased intestinal distention, activity is gradually decreased so that at 30 mm. Hg. motility ceases. Antiperistaltic activity above the site of the obstruction is considered by some to be due to a marginal current set up by the muscularis mucosa; Others maintain that the intestinal musculature can conduct peristaltic waves in either direction.

(d) *Local circulatory disturbances.*

The possible causes of impaired circulation in an obstructed bowel may be due to any of the following; distention, interference with the flow of blood in the

mesentery, increased peristalsis, disturbed vasomator action, increased intra-abdominal pressure, or impaired systemic circulation.

In clinical intestinal obstruction, injury to the bowel is due chiefly to distention and venous occulsion. Increased intra-enteric pressure results in decreased circulation of the bowel wall. Blood flow almost ceases when the pressure reaches the diastolic blood pressure; Complete stoppage occurs when the systolic pressure is reached. This result is evident when the anatomical relations of the blood supply of the small and large gut are appreciated. The arteries and veins pass through the circular muscle coat; they are very prone to be occluded in passing from the subserosa to the submucous plexus.

According to Gatch and Culbertson, violent peristalsis causes arterial relaxation and increased blood flow to that segment of bowel. This increased circulation leads to congestion of the bowel above the obstruction.

Increased abdominal pressure has little influence on the circulation of obstructed bowel. However, impaired systemic circulation aggravates an already impaired blood supply to the bowel. Intestinal distention has very little effect on the remaining intra-abdominal circulation. Oppenheimer and Mann showed that there was no effect on the capillary circulation in bowel wall with ordinary range of pressures in clinical obstruction.

(e) *Effect on the permiability and viability of the bowel wall.*

Sustained intra-enteric pressures of adequate intensity and duration result in abnormal permiability and loss of viability of the bowel wall. The greater the intensity, the less the duration to produce the same effect. Varying degrees of petechial haemorrhages, congestion and necrosis are seen.

(f) *Absorption in obstruction.*

The rapidity of absorption of substances such as strychnine, histamine, saline and dextrose is reduced to a marked degree over a peroid of 15 hours following obstruction with distention. Braun and Borattan showed that if the distention of a isolated loop in which strychnine was placed was relieved, death occurred immediately from poisoning. This data suggests that aspiration decompression of distended loops at operation is harmful because of the possibility of releasing a toxic exudate into the blood stream. For the same reason, the return of a loop of bowel which has been strangulated, into the peritoneal cavity is to be debated. Water absorption in the lower obstructed ileum is decreased by 90% of normal.

Since the rate of absorption is governed by the osmotic pressure of the fluid within the bowel lumen and by the volume of circulating blood through the intestinal wall, there will be a gradual decrease in absorption rate as intraluminal pressure rises to the diastolic blood pressure. At this level absorption via mesenteric vessels ceases and trans-peritoneal absorption begins. The absorption of abnormal constituents occurs only when the mucosa becomes devitalized and permits the passage of toxic substances. Increased amounts of non-viable bowel increases the rate of absorption due to abnormal permiability.

The avenues of absorption are through the mesenteric lymphatics or venous radicles or through the peritoneum. Experimentally increased intraluminal pres-

sure results in increased lymphatic absorption. Positive cultures of bacteria from lymph nodes were obtained.

III. Electrolytic Disturbances.

Interchange between plasma and extra-cellular fluid is free. The degree of hydration is reflected by the status of the interstitial fluid. Dehydration causes anhydremia.

High obstruction leads to severe vomiting; the result is a concentration of plasma; total interstitial fluids is decreased leading to varying degrees of dehydration. Na. is the principle cation of the plasma and interstitial fluid. Na. loss results in a temporary hypotonicity of plasma and interstitial fluids. To restore equilibrium, urine is excreted with a low concentration of electrolytes and water passes from the extra-cellular fluids into the cells.

In pyloric obstruction, vomiting produces a loss of gastric juice with greater loss of chloride than sodium. This leads to alkalosis with rise in plasma bicarbonate, lowering of the plasma chlorides and dehydration with oliguria and rise of N.P.N. Chlorides are replentished by saline administration and excess sodium is excreted in the urine.

In duodenal or high jejunal obstruction, the pH of the secretions is almost that of plasma. The loss of base and acid ions by vomiting is about equal. The effects are those of dehydration.

In low small bowel obstruction, the typical blood chemistry changes seen are infrequently due to electrolytic and fluid loss by vomiting and inadequate absorption of fluid from the distended gut. McIver and Gamble showed that the degree of body water loss can rarely be estimated from the plasma chloride level. Furthermore it has been shown that the blood chemistry may be normal even when dehydration is severe.

IV Dehydration.

Davis (1941) discusses the pathology of what he calls dehydration shock. Acute experimental loss of water causes hemoconcentration. This is reflected by the increasing viscosity of the blood, producing an anoxemia of body tissues with dilatation and increase permeability of the capillaries.

The importance of the elevation ofthe N.P.N. in intestinal obstruction has been stressed by Falconer. He states that the rise in the blood urea is the only biochemical change that is constantly found in obstruction at all levels. The N.P.N. of the blood will remain constantly elevated until the obstruction is relieved, no matter if all other biochemical changes are brought to normal.

The values of the N.P.N. are variable, in many cases doubled or greater, and is mainly made up of urea. Many suggestions attempt to explain this rise.

1. Massive necrosis and breakdown of body tissues associated with strangulation has been suggested. However, Dragstedt showed that there may be a great amount of tissue degeneration and absorption without rise.

2. Dehydration with resulting blood concentration is another possibility, but in many cases while the urea concentration is increased by 100%, there is no blood concentration.

3. Brown, Fox and Whipple advocated that impairment of renal function resulted from the action of an absorbed toxin. Recent work has shown that the pathological changes seen occassionally in the kidneys is due to dehydration and not toxemia. Furthermore, nitrogen excretion in the urine in cases of obstruction may reach 4-5 times normal.
4. Some suggest that is is a toxic destruction of protein and amino acids with increased formation of N.P.N, products.
5. Graham believes that it is biochemical in origin with no basis in organic renal disease.

The question is, as yet, controversial. One or more than one of these factors may play a part in promoting the rise.

Changes in the liver and adrenals have been reported by some observers. Elman and Cole have demonstrated a mild central necrosis of the liver in nearly all dogs with simple occlusion. Scudder, Whipple and Wahl have found consistent adrenal cellular changes and lipoid depletion after death in experimental and clinical obstruction.

V. Circulatory Changes.

(a) Blood and Plasma Volume.

Ender and Herrin with experimental obstruction in the upper portion of the jejunum found (1) a blood haematocrit of 23-40%; (2) a plasma volume decrease of 23-29%; (3) an extracellular fluid decrease of 19-34%. They conclude that loss of sodium, chlorides and water into the obstructed bowel leads to reduction of the plasma and tissue fluid volumes with resulting circulatory failure.

Fine, Hurvitz and Meill state that distention of the small intestine leads to circulatory plasma loss of 12-25%. As the plasma volume falls the haematocrit rises. This increase is far greater than can be explained by dehydration, however severe. They conclude that the extent of plasma loss is proportional to the degree of distention and have found that effective decompression of the small intestine restores the plasma volume toward normal. Great alterations in plasma volumes can occur in the absence of distention, due solely to dehydration over long period of time. It is of the greatest importance to recognize that the basic change in the character of the fluid loss in simple occlusion is a loss of blood plasma without a loss of cells.

(b) Scott and Wangenstien (1932) experimentally showed that venous obstruction produced haemorrhagic infarction of the bowel wall and calculated a 55% average blood loss. The loss of blood was sufficient to account for shock and death. In arterial obstruction there was a 20% blood volume loss, most of which was due to loss of plasma. Incarceration with arterial and venous occlusion gave results intermediary between the above two. Thus, in clinical strangulation obstruction with venous occlusion, there is a decrease in the circulating blood volume; this decrease is not only due to plasma loss but also to cell loss up to 50% of the total. This tremendous cell volume loss simulates massive internal haemorrhage leading to severe anaemia.

In venous strangulating obstruction, the capillaries of the bowel wall are subjected to the full force of systolic pressure. The otherwise rapid destruction of the capillary wall is prevented by increasing tissue tension about the capillaries. Early in the process of strangulation there is a loss of contractility and power of absorption.

When transperitoneal absorption occurs, the bacteriology of the peritoneal fluid yields positive cultures in almost all cases, the organisms being both aerobes and anaerobes. Toxic products are not present in the peritoneal fluid except terminally when loops become gangrenous or rupture.

Evans presents the factors in the mechanism of shock in strangulation. In strangulation due to venous occlusion, there is local increased capillary permeability with local loss of plasma. Plasma volume falls, cardiac output decreases with general anoxemia of body tissues resulting in widespread increased capillary permeability. Blood pressure falls and a viscious circle is established.

VI. The Systemic Manifestations of Distention.

Distention causes (a) circulatory changes manifested by elevation of venous pressure of the ankle veins and stasis in the lower extremities and (b) immediate reflex responses—the impluses set up by distention travel by way of the afferent fibres of the splanchnic nerves. In distention there is arrest of respiratory rhythm.

B THE CAUSE OF DEATH.

In the literature there is conflict of theories and even of experimental evidence. This is due partly to the complexity of the subject. Intestinal obstruction is not a single disease but a group of diverse diseases: a theory of the cause of death in duodenal occlusion is not applicable to volvulus of the sigmoid colon. Thus each type of obstruction must be studied separately; the more exact our pathological classification is, the more accurate our observations and deductions are likely to be.

Obstructions may be classified as follows:

(a) Simple occlusion 1. high small intestine.
2. low small intestine.
3. colonic.

(b) Closed loop obstruction.
1. sterile loops.
2. heavily infected loops.
3. mildly infected loops.

(c) Strangulation 1. short medium and long loops.

Simple Occlusion.

1. *High small intestinal occlusion.*

All the phenomena depend on the loss of H20 and inorganic ions which are poured into this obstruction, is, according to Besser, due to loss of chlorides and sodium and with them H20. Gamble and Ross showed that there is a lowering of the sodium content of the serum. The sodium loss is more significant then the chloride which is replaced by bicarbonate. The sequence of events in pyloric

obstruction is—distention of the stomach—dehydration—demineralization with sodium, chloride and potassium disturbances—alkalosis—azotemia. Death in experimental high obstruction is due to the loss of water and electolytes with dehydration and disturbed acid-base balance.

2. *Low small intestinal occlusion.*

In this form of obstruction, the precise cause of death is unknown. It is possible that it may vary from case to case.

Sodium and H20 loss may be a factor in some cases, but cannot be responsible for the majority of cases. In late stages dehydration in often slight, and it is rare to find a reduction of more than 25% in blood chlorides.

Perforation and peritonitis is not commonly seen in man because operation is performed before perforation occurs.

Herrin and Meill (1933) placed ballons in Thiry loops and Thiry-Villa fistulae producing distention of the loop or fistula without obstruction to the main intestinal stream. They concluded that distention causes vomiting by a nervous reflex pathway, which also leads to a loss of appetite; death occurs from an unbalanced chloride loss. Taylor and his associates disproved that blood chloride depletion is the primary cause of intoxication.

Taylor, Weld and Harrison, in their experiments on distention without occlusion of the upper jejunal segment, postulated that distention is the primary cause of death in intestinal obstructions. Afferent nerve impluses from the distended viscus cause vomiting, fall in blood pressure, and collapse.

Fine, Rosenfeld and Guedel point out that the distention pressure was far in excess of that seen in man. However, they acknowledge that the neurogenic factor cannot be ignored.

Splanchnic congestion with pouring of blood and plasma into the wall of the bowel above the site of the obstruction leads to a depleted circulatory blood volume. But the loss of blood and plasma in the oedematous and congested bowel is not adequate to cause death.

The work on toxic factors consisted of isolating such substances as choline, neurine, heteroproteose, nucleoprtein. histamine and a great number of others from the contents above the obstruction and trying to prove that these cause symptoms and terminal collapse.

Recent experiments show that both normal and obstructed contents are toxic. No toxin has ever been demonstrated in the blood, nor is the theory supported by cross circulation experiments. It is only when the viability of the bowel is decreased when it becomes permeable to various toxic elements and bacteria. The work of Blaine and Kennedy re-established the important role that bacteria play in the toxemia and death in strangulating ileal obstructions. Penicillin prolonged life in cases of strangulated obstructions, provided that other therapeutic measures were employed to combat haemorrhage, shock, chloride and water loss. Using isolated loop obstructions, Harper and Blaine concluded that the intestinal wall, injured by distention, becomes infected by the normal bacterial flora. They believe that bacterial infection and distention are responsible for toxemia and death.

Scuddle and Zwemmer and Whipple reported a lethal rise in blood potassium in simple obstruction, strangulation and gangrene. Keith and Buerger raised the blood potassium in a group of normal people with no harmful results. In experiments with dogs, Greenwood, Haist and Taylor concluded that hyperpotassemia is of little importance as the cause of death.

Starvation as a factor in morbidity has received insufficient attention. Because of the mass of biochemical and physiological detail, the importance of this factor is obscured. Lack of protein is the important element in starvation because of marked protein loss in all cases of obstruction.

The results of many workers emphasize the mechanical factors in the development of the ill effects of intestinal obstruction. The chief concern is the viability of the bowel wall which may be threatened by external constricting agents or increased intra-enteric pressure. The importance of swallowed air in initiating distention and its effects has been outlined. Transperitoneal absorption occurs through impaired bowel wall. If the bowel is viable all absorption from the gut is diminished, except through the lymphatic channels. Thus, the chief lethal factor in simple low ileal obstruction is permeation of a gut wall whose viability has become impaired, by bacteria or other agents.

3. *Colonic occlusion.*

Colonic occlusion is more serious in man than in animals because it is usually an acute episode of a prolonged chronic state, with dilation and hypertrophy of muscle of bowel wall and stercoral ulceration. In untreated cases with high colonic pressures, perforation occurs at the site of ulceration.

(b) Closed loop obstructions.

1. With sterile contents—the loop dilates gradually due to mucous, but with no systemic effects.
2. The organisms of heavily infected loops multiply and the sequence of events and gas formation leads to pyocele. There is interference with local circulation, resulting in impaired viability of wall with perforation and peritonitis.
3. In mildly infected loops the same changes occur as above, but distention is very great due to fluid and gas accumulation with congestion and oedema of the bowel wall. The pressure within the loop may reach enormous levels so that strangulation may occur from closure of the vessels in the wall.

(c) Strangulation.

1. In short loops, death is due to rupture with peritonitis.
2. Long loop strangulation is seen in superior mesenteric artery occlusion. An enormous volume of blood is lost into the lumen of the bowel, peritoneal cavity and congested bowel wall. The animal dies in a few hours of massive internal haemorrhage.
3. In medium loops the blood loss is not sufficient to account for death. If one-fortieth of the bowel is strangulated, there is no alteration of blood plasma or volume at time of death. If one-twentieth is strangulated, there is a 15% reduction in blood volume.

Foster and Hauser surrounded an isolated strangulated loop with a rubber bag, restoring the continuity of the intestines; the collected fluid injected into an animal was toxic, the toxic element consisting of immediate transudation with products of abnormal tissue metabolism and late addition of toxins of bacterial origin. The toxicity of the transudate depends on the number of infective bacteria within the loop, as well as the duration of strangulation. In the earlier stages when the peritoneal transudate is not yet toxic, the outer layers of the bowel wall are sterile, as is the transudate. When the fluid is toxic, the sero-muscular coat gives positive cultures. This may be the factor in cases fortified pre-operatively, operated on with little trauma, and post-operatively have falling blood pressure rising pulse and pallor—the manifestations of toxemia. Death in medium loop strangulation results from infection of devitalized bowel by bacteria from the lumen, and absorption by the peritoneum of toxic products of growth.

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ISOTOPIC TRACERS IN MEDICAL RESEARCH

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Although Hevesy and his associates developed tracer techniques between 1920 and 1930 using naturally radioactive elements or stable isotopes of lead arising from them, practically all the experimental studies made with labelled atoms have taken place since 1932 when Urey and his associates began separating isotopes of light stable elements, and since 1934 when the Curie-Joliots discovered that isotopes of stables elements could be rendered radioactive. Although this field of research is young it is rapidly assuming a position of importance in the medical sciences. The following paper is written with the objects of defining terms and stating principles basic to work in this new field, and to indicate ways in which such principles apply to tracer methods in physiology and biochemistry.

The Nature of Isotopic Tracers

All of the elements of which all matter is composed are made up of *atoms.* The basic particles of which all atoms are at present believed to be composed are (a) the *proton,* a positively charged particle which has been found to be identical with the nucleus of the ordinary hydrogen atom; (b) the *neutron,* a particle having a mass approximately the same as that of the proton but havinb no electrical charge, and (c) the *negative electron,* a particle having a mass amounting to approximately *0.05%* of that of a proton, and an electrical charge equal in magnitude but opposite in sign to that carried by each proton. All atomic nuclei are composed of combinations of protons and neutrons, the electrons only appearing in that part of the atom lying outside of the nucleus.

Two important quantities characteristic of the nucleus of any atom are: its *atomic number,* which may be defined as the number of protons within the nucleus, and its *mass number* which represents the sum of the protons and neutrons which make up the nucleus. Of these two quantities, the former determines the number of electrons which circulate about the nucleus of the neutral atom, while these in turn determine the chemical properties characteristic of the elements considered. The mass number is a fairly close measure of the atomic weight of the atom considered. The atomic number is commonly indicated in the symbol representing a given type of atom by a number placed before the symbol of the element considered, while the mass number is represented by a number placed after the symbol. For example, the rare stable isotope of carbon having mass number equal to thirteen is written as ${}_6C^{13}$ or sometimes simply as C^{13}.

When a change occurs in the atomic number or mass number of an atom due to any cause, it is said to be *transmuted* from one chemical element into another. If its mass number is changed while the atomic number remains constant, the mass of the atom is changed although its chemical nature remains the same. Two such atoms are know as *isotopes* of the same element and, since they have the same electronic configurations, might be expected to have indistinguishable chemical properties in spite of their difference in mass. It is upon the premise that isotopes

*A unit of strength widely used in the past is the *curie,* representing the strength of a source having approximately 3.7×10^{10} atomic disintegrations per second.

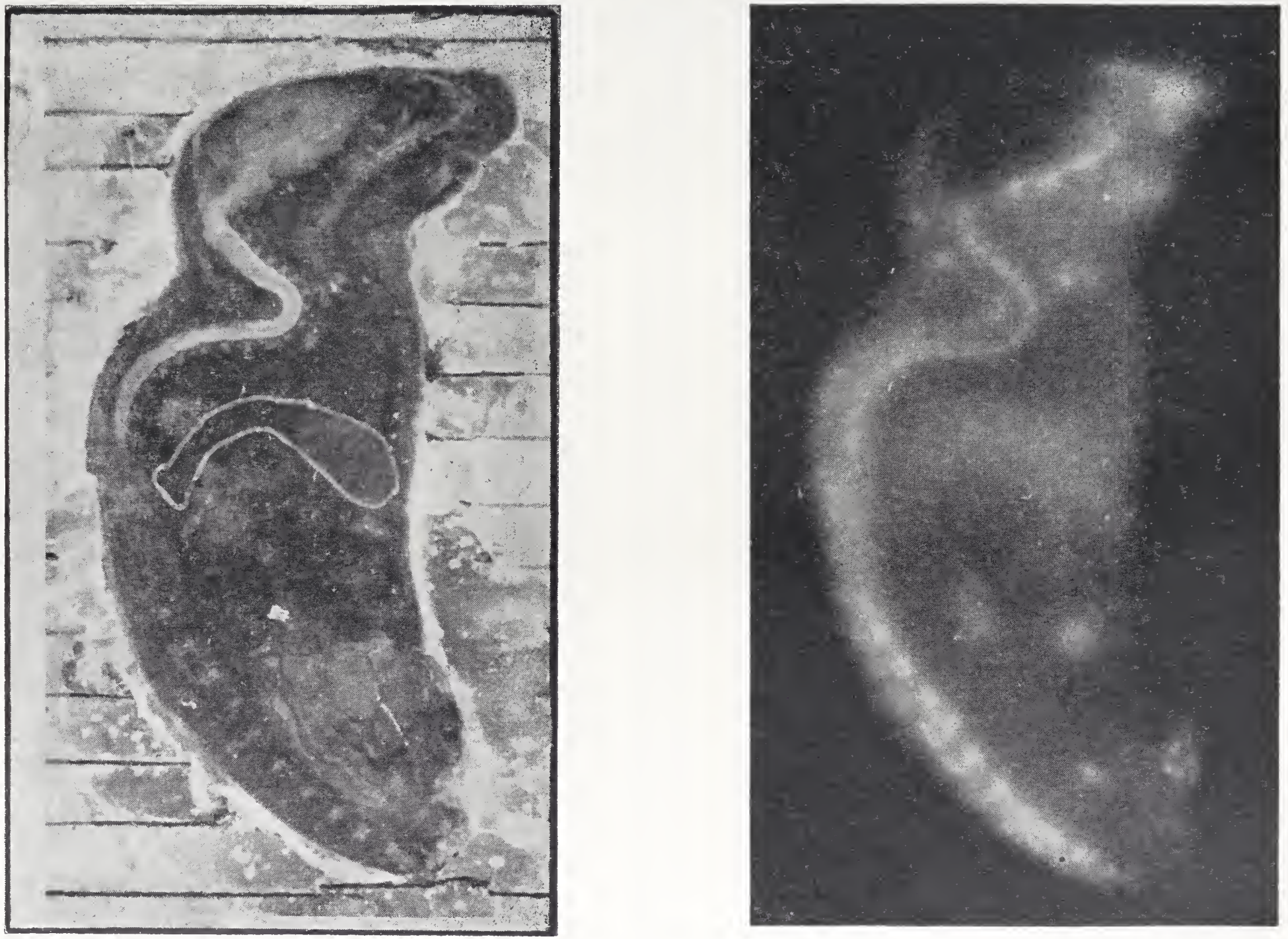

FIGURE I: Photograph and Radio-Autograph of a Sagittal Section of an Alloxan-Diabetic Mouse Injected with $_{15}P^{32}$ as Na_2HPO_4. Note Localization of $_{15}P^{32}$ Particularly in Teeth, Epiphyseal Bone, Liver (outlined) and Intestinal Walls.

of the same element are chemically indistinguishable that all work using them as tracers is based.

The veracity of the above fundamental premise has been tested by many different workers studying a number of different isotopic combinations in an assortment of chemical forms. The most extensive and, for the present discussion, the most important work has consisted of measurements of the relative abundance in nature of stable isotopes of hydrogen, carbon and nitrogen in various chemical combinations. As a result of such tests, it is generally conceded (1, 2) that the magnitude of isotopic separations found to occur spontaneously in animate and inanimate nature is too small to prevent general application of the basic premise that isotopes of the same elements are chemically indistinguishable.

There are two ways in which isotopes are prepared for use as tracers: (a) by the concentration of a stable isotope of an element, the concentrated isotope being normally rare as found in nature;

(b) by inducing radioactivity into isotopes of otherwise stable elements.

Concentrated stable isotopes are identified in tracer work by the difference in their relative abundance in samples of tracer material from that in an unmodified mixture of unseparated isotopes of the same element. Since, as was indicated, such isotopes are chemically and biochemically indistinguishable such differences in their relative abundance must be measured by means of a difference in some physical characteristic. The differences in mass of the isotopes is generally employed for this purpose, using a mass spectrometer or various densimetric instruments. Slight but characteristic differences in indices of refraction of isotopes have also been employed to measure their relative abundance.

Radioactive isotopes have the unique property of having unstable nuclei each of which will at some future time disrupt, emitting an ionizing particles. It is this property which makes them particularly valuable as tracer atoms since they are detected by these ionizing radiations. The radiation emitted generally consists of beta- and gamma-rays. Only one beta-ray (and possibly a gamma-ray) is released at the end of the life as such of each radioactive atomic nucleus and, aside from this single transmutative disruption, a radioactive atom does not differ chemically from a stable atom of the same element.

The *strength* of a given radioactive source is defined as the rate at which nuclei in the source are disrupting and releasing their rays. The *rutherford** is a unit of radioactive strength representing the strength of a source having 10^6 disintegrations per second. *The rate of disintegration of the atoms of a radioactive isotope is in every case proportional to the number of radioactive atoms present, the proportionality factor being characteristic of the radioactive isotope.* In mathematical form this statement can be written:

$$\frac{dN}{dt} = -kn \qquad (1)$$

Integrating,

$$N = N_o e^{-kt} \qquad (2)$$

where N represents the number of radioactive atoms present at time t, N_0 being the number present when $t = 0$. The value of the constant k is characteristic of the radioactive isotope being considered, while e is a universal constant which, stated to four figures, has the value $e = 2.718$.

It is seen that as time goes on the number of non-distinguishable radioactive atoms decreases exponentially (Figure II) The time T taken for half of any initial number of atoms to disintegrate is called the *half-time* of that radioactive isotope, and is a fundamental characteristic of it related to the constant k as shown in equation 3:

$$T_{\frac{1}{2}} = \frac{0.693}{k} \qquad (3)$$

Tracer Methods Applicable to Physiological and Biochemical Problems:

(i) *The isotopic dilution method*

Rittenberg (1) has pointed out that most chemical methods of analysis involve procedures whcih completely separate the particular substance which is being analyzed. While such methods of analysis are available for many inorganic substances, corresponding methods for complex organic compounds are, in general, not well developed. However, at the present time it is frequently possible to isolate from a mixture of such compounds either all of a component compound in an impure state or some of the compound in a pure state. The isotopic dilution method provides a relatively straightforward means for determining quantitatively the total amount of a pure organic substance in such a mixture of organic substances.

As an example, suppose it is desired to estimate the amount of an amino acid in a certain protein. A known mass W of the synthetic amino acid containing stably-bound carbon or nitrogen tracer at concentration C is added to the mixture obtained by hydrolysis of the protein into its constituent amino acids. After sufficient time is allowed to permit the added amino acid to become thoroughly mixed with the hydrolysate, some of the test amino acid is isolated from this mixture and purified, and its concentration of tracer, C , measured. Since the amount of labelled amino acid which was added now represents the only fraction of that amino acid in the mixture which is labelled, it follows that:

$$C_a W_a = C_b (W_a + W_b) \qquad (4)$$

from which the total mass W of the test amino acid which was present in the protein hydrolysate before the labelled amino acid was added can be determined. It is noted that the amount of the amino acid isolated from the mixture does not enter into equation 4. Rittenberg and his associates have used this method in determining the percentage distribution of many amino acids in the protein fibrin, this being only one example of the very wide field of its potential applicability.

(ii) *Determination of whether or not specific chemical compounds form an intermediate link in transformations in the living body.*

An excellent statement made by Kamen (3) regarding use of tracers for this purpose is quoted below:

"The hypothesis that a particular compound occurs as a fleeting intermediate in a complex biochemical process can often be established by adding an unlabelled sample of this compound and allowing the metabolism of a labelled substrate to occur. If the hypothesis is correct, re-extraction of a sample of the added compound will result in finding it labelled, because the 'labelled' intermediate produced in the metabolic process will have mixed with it before being consumed in the next step of the reaction. For example, in mammalian liver and kidney, fatty acids are observed to be converted through aceto-acetate."

(iii) *Study of the normal metabolism of trace elements in the body.*

It has been well established that a number of elements such as iron, copper, manganese, zinc and cobalt are essential to the metabolism of certain organisms, but are present only in trace amounts (less than one part in a million). These are often difficult to detect any very difficult to measure quantitatively even using micro-chemical methods. However, where *radioactive* isotopes of such elements are available and can be obtained with high specific activity they provide an effective tool for carrying out quantitative studies in view of such trace elements, since only physiological amounts need to be administered. This use of radioisotopes has already resulted in substantial addition to our knowledge of the metabolism of such trace elements (4).

(iv) *Studies by means of radio-autography*

By means of the effects of the radiation from radio-active isotopes on photographic emulsions, it is possible to study the distribution of substances within the living body, using such isotopes as tracers. The current experimental procedure involves administration to the organism of a selected substance labelled with radio-active tracer. A cross-section of the organism is then placed in close contact with a suitable photographic emulsion, the radio-isotope producing a blackening of the emulsion over regions in the organism in which the radio-isotope has been concentrated. The photographic pattern obtained in this way is called a radio-autograph of the tissue section. A photograph of the section itself is then generally made and compared with the radio-autograph, thus providing a relatively simple method for identifying tissue structures in which the radio-isotope is preferentially concentrated.

This technique is proving to be of special value in studying the distribution of compounds in microscopic sections of tissues and in very small animals, such as insects. When used in larger animals it provides a relatively simple means of surveying the distribution of a compound before proceeding to more quantitative measurements on selected tissues (Figure I).

(v) *Measurement of reaction rates in the living body under condtitions of physiological equilibrium.*

It is probable that isotopic tracers will find their most important field of application in the measurement of reaction rates within the intact living body. The

mammalian body, for example, contains many systems in which a specific chemical compound is maintained at an effectively constant concentration in a metabolic pool by balanced rates of its supply to and removal from the pool. Among the body fluids blood sugar represents a familiar example of such a substance, while the phospholipids represent corresponding examples in body tissues. In a fraction of the molecules of such a compound are labelled but are chemically indistinguishable from those which are untagged, *the rate at which labelled molecules will be removed from the metabolic pool will be proportional to the fraction of the molecules in the pool which are so labelled.*

On comparison, this italisized statement and that preceding equations (1) and (2) are seen to be of the same form, and hence the fraction of labelled molecules in the above metabolic pool will fall exponentially with the time t if only unlabelled molecules are being added to the pool after some arbitrary zero hour, and the size of the pool is maintained constant. Under such an experimental condition it is possible to measure the half-life of the molecules in the pool by removing samples from it at a series of different times after zero hour and measuring what fraction of the molecules in each sample are labelled. The relation between f and t obtained by this procedure is the same as that between N and t stated in equations (1) and (2), and illustrated in Figure II, and is called an exponential decay curve.

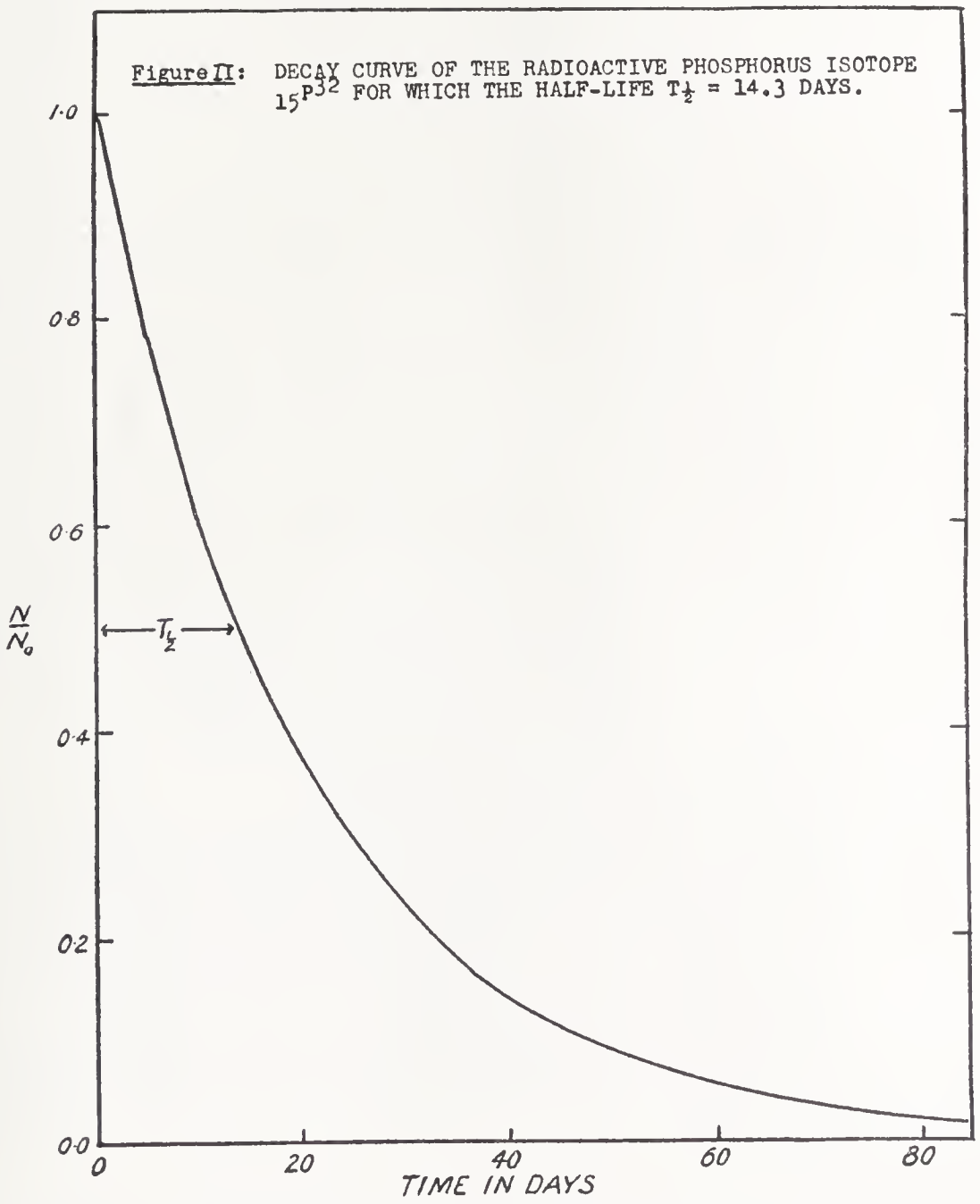

FIGURE II: Decay curve of the radioactive phosphorus isotope $15P^{32}$ for which the half-life $T\frac{1}{2} = 14.3$ DAYS.

Conversely it is possible to start with zero labelled molecules in such a metabolic pool at zero hour, and, while supplying labelled molecules to the pool at a constant rate, to determine the fraction of the molecules in the pool which are found to be labelled at a series of times thereafter. The "growth curve" relating these two variables can be shown to have the equation

$$f = f_m (i - e^{-kt}) \qquad (5)$$

in which all factors but *f* and *t* are constants, K having the same value as when determined by decay curve. The half-life of the compound in the metabolic pool is obtainable from the transformation constant K by a realtion similar to that stated in equation (3).

When in addition to the half-life (or the equivalent K-value) of a compound in a specific body tissue or fluid the equilibrium amount M of the compound in the metabolic pool is known, it can be shown (5) that the rate R at which that compound in the pool is being replaced is given by the following relation:

$$R = KM_o \qquad (6)$$

R is often referred to in the literature as the *turnover rate.*

An excellent example in which the first of the above methods of measuring turnover rate is applied to a normal blood constituent is seen in a paper by Zilversmit et al. (6), in which the rate at which plasma phospholipid is supplied to and removed from the blood of the dog is measured.

It cannot be too strongly emphasized that in this type of tracer study the methods are only applicable where conditions of *dynamic equilbrium* exist. For animals this will frequently limit its quantitative application to studies made on adults. If growing animals must be used the turnover rate of the component being studied should be short compared with its overall growth rate in the tissue being studied. Furthermore commencement or cessation of administration of labelled metabolite, whether by feeding or injection, must not disturb the previously existing condition of equilibrium. It is also possible that more than one tissue in the body will be contributing to or withdrawing material from a common metabolic pool. If the half-lives of the common material in such tissues differ appreciably, the one of longer half-life can modify the shape of the growth—or decay-curve of the one of shorter life. Some examples of this type of modification are indicated in the work of Ussing (7) with deuterium-labelled amino acids.

Limiting Conditions in the Use of Isotopes as Tracers

Certain basic conditions must be met before some types of experiment involving isotopic tracers can be sucessfully carried out. In the first place it must be possible to incorporate the tracer element into a non-labile position in the chemical required for the experiment. This has been accomplished successfully for a limited number of organic compounds having important functions in the animal body, especially using stable isotopes as labels where the time required for preparation of such compounds is not a limiting factor.

Secondly, it must be possible to detect and measure the abundance of the tracer element both at the start and finish of the experiment. In the case of radioactive tracers, detecting instruments such as the Geiger-Muller counter can be made highly sensitive, and the radioactive isotope can often be detected when present at only 10^{-8} of its original concentration. However, in experiments where considerable time is required before the final analyses are made, the associated fall in activity of the radio-tracer (illustrated in Figure II) limits its effective range of dilution. One might feel that this range could be extended by performing an experiment using a large amount of the radio-isotope in the labelled chemical. However, even if the availability of large amounts of radio-isotope were not a limiting factor, the amount which can be employed without producing appreciable abnormalities due to radiation effects places an upper limit on the initial dose which can be used. It has been estimated that, btween the limitations of the size of initial dose of radioactive isotope and the minimal intensity which can be detected after dluion in he experiment, an interval approximately six times as long as the half-life can be utilized for most radio-isotopes (8).

The magnitude of the dilution factor which can be successfully employed when using a stable isotope as a tracer is determined by the ability of the mass spectrometer or other means of detection to resolve differences from normal in the relative abundance of the rare isotope in the labelled substance after it has been mixed with a quantity of the substance which is unlabelled. The usable range of dilution will of course increase with the amount of labelled substance administered. In general, the smaller the relative abundance of a rare isotope in a sample of the element taken from nature and the greater its relative abundance in the initial tracer mixture, the larger is the range through which it can be diluted and still be detected. Deuterium has small relative abundance in natural samples (0.015%) and can be just detected after a 10^{-5} dilution of pure deuterium with a natural mixture of hydrogen isotopes, while pure ${}_{7}N15$, representing 0.38% of the total nitrogen found in nature, can only be diluted with natural nitrogen to 10^{-4} of its original concentration before it can no longer be traced. It is obvious that at the present time the radioisotopes have a much greater useful range of dilution in short-term experiments. On the other hand the stable isotopes have the advantage that when they are used as tracers time is not a limiting factor in their preparation and use to the extent that it is with practically all of the radio-isotopes. This bars most radio-isotopes from use in many important long-term experiments.

While the above circumstances place important limitations on the use of isotopes as tracer labels, their application in the methods described in this paper has produced outstanding advances in many branches of physiology and biochemistry during the past decade. It is reasonable to anticipate that they will continue to be of service in these fields in the future.

TREMOR IN DISEASE

By M. L. BLACK, 4T7

DEFINITION.

Tremor exists when the normally continuous contractions of a muscle at work, or the uniform tone of a muscle at rest are replaced by a succession of separately perceptible muscular twitches. Tremors will be discussed as (1) Fine Tremors; (2) Coarse Tremors; (3) Intention Tremors.

FINE TREMOR consists of regular or irregular oscillation of small amplitude. They should be distinguished from the fibrillar contractions of individual muscle fibres or muscle bundles seen in muscular degeneration. Only the common conditions in which fine tremor occurs will be discussed.

Senile Tremor; Senile tremor is due to senile degeneration in the basal ganglia. During sleep, the tremor ceases. It can be controlled temporarily by will or by support of the limb. This tremor is aggravated by fatigue, exertion and nervous tension.

Senile tremor is differentiated from Paralysis Agitans by absence of rigidity, pill-rolling movements, cramps, forward pitch, immobility and lack of facial expression.

There is no treatment which radically influences the condition thiamin chloride occasionally causes some improvement.

Paralsis Agitans; tremor is frequently the first sign of this condition; it is progressive and may become coarse. It is a to-and-fro tremor with with 3-8 excursions per second. Pill-rolling movements may be combined with flexion and extension at the wrist, and pronation and supination of the forearm.

Important in the diagnosis is the fact that tremor affects one half of the body before the other, beginning in one hand, spreading to the leg of the same side, and after months or years, similarily involving the opposite limbs. Movements occur at rest and may persist during sleep. (Senile tremor never does). The tremor may be decreased by will, or by active or passive movement. The tremor is increased by emotional stress. It may become coarse in long standing cases.

Grave's Disease; Fine tremor of the outstretched hand is one of the classical signs of this disease. The tremor is regular, rapid (8 per second), and of short amplitude. It is increased by exertion and excitement. Trembling of the whole body may occur in severe cases.

The mechanism of this tremor is not understood. It may be due to excessive glycogen in the circulation, caused by hyperactivity of the adrenal medulla, resulting in excessive muscular activity to the point of exhaustion and a change of the normal muscle tone to tremor.

Hyperinsulinism; Tremor begins in moderate hyperinsulinism associated with episodic weakness, excess perspiration, hunger and apprehension. Muscular twitchings may ensue with convulsions and coma.

Alcoholism; tremor after excessive ingestion of alcohol is fine, rapid and regular. The tremor is well demonstrated in the fingers of the outspread hand. In

delerium tremens, profound anxiety, acute confusion, hallucinations and marked tremor are common characters. These occur after a prolonged drinking bout with sudden deprivation of alcohol. They disappear in 4-5 days. The tremor is general but is most marked in the face, tongue and hands.

Occupational Neurosis, Hysteria and anxiety Neurosis; In some cases of occupational neurosis a tremor develops. A good example is writer's cramp. In the early stages the disability is limited to the single act in which the tremor originates. Later the tremor may extend to other acts carried out by the same hand. A woman with Writer's Cramp learned to use a typewriter. Her disability then extended to typing. Similarity, the sufferer from Writer's Cramp who learns to write with the left hand may develop a disability of her left hand.

Tremor in hysteria may be general or local, unilateral or bilateral, coarse or fine. The tremor is increased when the patient's attention is drawn to it and may be absent when the patient's attention is distracted. Hysterical involuntary movements may simulate chorea. In such cases movements do not usually involve the face.

Fear is the emotional reaction to imminent danger; anxiety is the reaction to a possible future danger. In these emotional states there is increased activity of the sympathetic nervous system with resulting tremor.

Coarse Tremor.

Coarse tremors may develop as exaggerations of fine tremors; thus the fine tremor of Paralysis agitans may become a coarse tremor. Coarse tremor may also occur in hysteria and general paresis.

Disseminated Sclerosis; Intention tremor associated with nysagmus and scanning speech are the classic symptoms of this condition. The head may oscillate when the patient is holding it up; the trunk may jerk while sitting or standing; the legs may jerk when standing or walking in a moderately advanced case. To differentiate hysteria from Disseminated Sclerosis there is a lack of definite signs and symptoms such as paling of the optic discs, nystagmus, Babinski's sign, and decreased sphincter control.

Chorea is characterized by involuntary rapid movements which are co-ordinated yet purposeless. The patient is in a state of constant motor unrest; his movements are non-rhythmic. The gait may be dancing or hopping. The three cardinal symptoms are spontaneous, purposeless movements, ataxia and weakness. Typically, there are involuntary but conscious, quick jerks and twitches of wide excursion. No two movements are of the same extent. These disappear during sleep unless very severe.

During examination of a mild case the choreic movements are commonly absent at first; later, when the novelty of the examination has worn off the involuntary actions gradually appear as though breaking through inhibition.

Intention Tremor.

Intention tremor is produced or exaggerated by voluntary movements. The limb is quiet when not in use but when voluntary movement occurs, irregular and

involuntary to-and-fro tremor is superadded to the intended movement. These motions become more marked as the objective is reached and may spread from the hand to arm or even the rest of the body. It occurs in lesions of the cerebellum, most commonly in Disseminated Sclerosis.

General Paralysis of the Insane; the tremor if present is a fine irregular oscillation, often twitching. It first appears about the lips and tongue. There is usually a slight slurring of speech. Late in the disease a coarse, general tremor begins.

Associated with the tremor are a moral and intellectual deficiency, tottering gait, decreased tendon reflexes, sluggish or absent pupillary light reflexes and general paralysis.

REFERENCES:

1. Rittenberg, D. Journal of Applied Physics *13:* 561, 1942.
2. Chaikoff, I. Physiological Reviews *22:* 291, 1942.
3. Kamen, M. Bulletin of Atomic Scientists *1:* No. 12:9, 1946.
4. Baudisch, O. American Scientist *31:* 211, 1943.
5. Zilversmit, D., Entenman, C., and Fishler, M. Journal of Gen. Physiology *26:* 325, 1943.
6. Zilversmit, D., Entenman, C., Fishler, M., and Chaikoff, I. Journal of Gen. Physiology *26:* 333, 1943.
7. Ussing, H. Acta Physiolog. Scand. *2:* 209, 1941.
8. Smith, S., and Cowie, D. Journal of Applied Physics *12:* 78, 1941.

Feature

C. L. RODGERS, Editor

THE GRENFELL MEDICAL MISSION

R. B. SALTER, 4T7

It has been my privilege to spend two very interesting summers on the Newfoundland coast with the Grenfell Medical Mission and having been asked by the Journal staff to write a short article on the subject, I am pleased to take this opportunity to make the work of the Mission a little more widely known.

The medical problem of the deep sea fishermen and their families along the bleak coasts of Northern Newfoundland and Labrador has been one of the most serious in the world. Had it not been for the lifework and inspiration of Sir Wilfred Grenfell,* whose firm belief in practical Christianity brought him to these desolate coasts some fifty years ago, these unfortunate fisherfolk would have virtually no medical care.

FIGURE I: A Labrador Fisherman's Home

Dr. Grenfell received his medical training in the famous London Hospital, and under the influence of the Surgeon-in-Chief, Sir Fredrick Treves, he entered the service of the Royal Mission to Deep Sea Fishermen and spent three years in the North Sea fishing fleet. Grenfell was then chosen to head an expedition to Labrador to begin the first real medical care for the fishermen who had come across the Atlantic to stay. Beginning by clothing the naked and treating the sick, he gradually achieved — by judicious charity, encouragement of thrift, and incitement to self-help and industry — an almost miraculous improvement in the existing conditions. To-day, the Grenfell Mission, more properly known as the International Grenfell Association, extends along one thousand miles of coastline, operates six hospitals, three nursing stations, two orphanage homes, and three ships, with a permanent

*Wilfred T. Grenfell, M.D., F.R.C.S., K.C.M.G., L.L.D. 1865-1940

staff of doctors, nurses, and social workers supplemented by a summer volunteer staff. The Association is international in the sense that its staff, as well as its financial support, come from the British Isles, the United States, and Canada. It is entirely independent of the Newfoundland government and has a Board of Directors in New York. Headquarters of the Mission is at St. Anthony, a fishing village of 900 inhabitants, at the northern tip of Newfoundland.

The people of northern Newfoundland and Labrador live in scattered small fishing villages along the rugged coast. Since there are neither roads nor railways in these northern areas, the only mode of travel is by boat in the summer and dog-team in winter. This is one of the factors which render medical work along the coast rather difficult. The land is so rocky and barren that agriculture is practically impossible and since there is not enough vegetation to nourish cattle, goats are kept by some for milk supply. It is not difficult to realize then, how inadequate is the diet of these people — the three main constituents of which are tea, bread, and fish

FIGURE II: Grenfell Hospital, St. Anthony, Newfoundland

— and evidence of avitaminosis is present throughout the populace. The very miserable, crowded living conditions in small houses combined with an inadequate diet from birth make the Newfoundlanders very susceptible to tuberculosis and indeed, the incidence of this disease in Newfoundland and Labrador is one of the world's highest. This is even more marked amongst the Eskimos of Northern Labrador.

The fisherman from Northern Newfoundland and Southern Labrador is of British origin but centuries of barehanded battle with the sea and of lonely existence in bleak coastal villages have made him rawboned in both body and mind so that he is a rugged individualist. He is relatively uneducated, primitive, hard working, self-sacrificing and very hospitable. His livelihood depends on fishing and on fishing alone, which explains his relative poverty. His method of fishing has not changed materially in the last fifty years and consists of "jigging" with a handline from a dory or small open motor boat within a few hundred yards of shore. This method

is, of course, painfully slow and arduous, and considering the short season, it is small wonder that the fisherman has difficulty providing for his family.

Dr. Grenfell early realized that these people needed more than medical care. They needed clothing, food, education and economic advice. Hence, Grenfell organized "clothing stores" on each of the medical stations. To these stores are sent serviceable clothes by Americans and Canadians to be distributed by the mission social workers. "Industrial shops" at the various stations are managed by occupational workers who supply material and teach the fishermen's wives to make hooked mats, woollen clothing, parkas, and leather goods (seal skin) which are sold in fashionable stores across Great Britain and North America. Likewise, invalided men unable to carry on the arduous deep sea fishing are taught to carve pins and ornaments out of ivory which is obtained from walrus tusks and whales' teeth. Economic advice is supplied through Fisherman's Co-operative, a recent innovation which is striving to eliminate the greedy middle man from the fish trade.

The education of Newfoundland and Labrador children is a very difficult problem indeed. The relative lack of qualified teachers, the widespread distribution of small groups of children, and the inadequate travel facilities combine to make the education very meagre. However, at St. Anthony the Mission provides a very fine school which accommodates 180 pupils who are able to proceed to Grade XI. Eighty of these school children are orphans who are cared for in the Children's Home by competent social workers. The more promising of the older students are sent out to the United States where further education is made possible for them on the understanding that they return to help their less fortunate fellowmen. For instance, the X-ray technician of the main hospital in St. Anthony obtained his training by this scheme and is at present rendering invaluable service. Likewise some of the girls are trained as nurses' aides in St. Anthony and later sent to England or America to become graduate nurses.

The Mission has erected a marine railway or ship haul-up at St. Anthony so that fishing schooners with damaged hulls may be taken up out of the water and repaired. Consequently these ships are soon back at their fishing and the necessity of having to limp all the way to St. John's is obviated.

The headquarters for the medical work of the Grenfell Mission is also at St. Anthony and consists of a 60-bed hospital which is well equipped, well kept and extremely well run. There is also a 20-bed sanatorium and a 20-bed convalescent annex. Dr. Charles S. Curtis, originally from Boston, has spent nearly thirty years on the coast and is the Superintendent of the entire Mission. As well as being an excellent administrator he is considered by many as one of the best surgeons in North America. Dr. Curtis has a variable staff from year to year but at this main hospital he usually has one or two other doctors with him. Each summer a volunteer medical student from Canada or the United States is taken on the staff and it was in this capacity that I enjoyed busy and interesting summers. The head nurse, Miss Carlson, has been with the Mission for many years and is most efficient. The nursing staff which usually numbers from six to eight is about equally divided between British, Canadian and American girls and the hospital also employs full time

laboratory and X-ray technicians. The surgery performed includes such varied operations as repair of hare lip and cleft palate, arthrodesis of tubercular joints, cholecystectomy, partial gastrectomy, thoracoplasty and Caesarian section. The hospital library is kept up to date with current medical publications and the standard of all work done is high. A very necessary part of the hospital is the dental office since Newfoundlanders have notoriously poor teeth. During my first summer at the hospital there was no dentist available and it became the task of the volunteer student to pull some 300 teeth under local anesthesia during the course of the summer. Last year the Mission was fortunate in having the services of Dr. Edward Daunton, a Toronto ex-army dentist. Refractions are also carried out at the hospital and a large supply of good glasses is kept to meet the great need. An illustration of the lack of education of people from the smaller fishing villages is given by the young man facing the Snellen Eye Chart who said, "I can see the letters but I just can't tell you what they spell".

The Mission has smaller hospitals at Northwest River, Cartwright, St. Mary's River, Forteau and Harrington, all on the Labrador coast as well as three nursing stations. It was at Cartwright that Archie MacKinley, one of my classmates, spent the summer of '45 as a volunteer medical student. Coastal mail boats bring the patients from their respective fishing villages to the nearest hospital and the more serious patients are referred to St. Anthony. During the summer months, a mail boat arrives approximately every eight or ten days and may bring as many as thirty patients. In emergencies however, a patient may have to be brought many miles through stormy seas in a small open motor boat.

The dialect of the Newfoundland and Labrador people is rather characteristic. For instance they use the word wonderful in a peculiar sense saying "I have a wonderful bad pain" or "It aches something wonderful." Consequently, when on early morning rounds a patient says "I had a wonderful night," one must be careful to act accordingly. "Scattertime" means 'occasionally' and the fisherman says "Scattertime I get headaches" or "I get a scatter headache," which is in effect quite expressive. When a patient says "I can't glutch" he means he has difficulty swallowing but when he says "I'm taken over with the shootin' miseries," it's a little difficult to know what he means. One poor old fisherman when asked on arrival at hospital if he had brought any belongings said, "I have neither thing but what I'm stood into."

Superstitions about medical phenomena amongst the fisherfolk have to a large extent been eradicated by the work of the Mission. However, even today in some of the lonely settlements one finds elderly women who "charm" aching teeth (and get at least temporary subjective results) or who advise the application of weasel skin to open wound surfaces to keep out infection."

Each summer the Mission sends the "Maraval", its 70 foot auxiliary schooner along the coast as a travelling clinic to visit the hundred or more tiny fishing villages from the most northerly Eskimo settlement in Labrador to the southern end of the Grenfell territory in White Bay, Newfoundland. This sturdy little ship is equipped with a very compact clinic and examining room and the trip is made

for the purpose of diagnostic investigations, minor surgery, dispensing of medicines and extracting teeth. During one trip in the summer of '45 we saw nearly 500 patients in a period of eight days. It was abroad the "Maraval" that Bill Lawler, another classmate, spent most of last summer, along the Labrador coast. During the winter, trips are made to the outlying villages by dogteam as often as possible and occasionally, major surgery is of necessity performed in a fisherman's home. It is interesting to note the number of persons who receive medical care from the Grenfell Mission. During the year of 1945 the Mission treated 1,500 in-patients, 12,000 clinic patients and made over 6,000 home visits.

Today, the work of the International Grenfell Association — medical, educational and social — is continuing on a larger scale than ever before. Although Sir Wilfred Grenfell passed away in his 65th year in 1940, his name will always be remembered by the thousands of people he has helped directly or indirectly and the spirit of his work remains. After many years on the coast, Sir Wilfred himself wrote in one of his books, "I would not have lost the opportunity of going to Newfoundland and Labrador for anything. Love is the force, the dynamic by which God enables us to serve and save the world. He works through us in the common things and common ways of life."

It is sincerely hoped that this short article may, in some measure, stimulate the interest and sympathy of fellow medical students, not only toward the people of Newfoundland and Labrador, but also toward all those living under such unfortunate circumstances.

FIGURE III: *Clinic Ship "Maraval"*

A MEDICAL STUDENT'S EXPERIENCES

S R. FRANKLING, 4T9

For the guidance of those students considering employment in a hospital laboratory during summer months, the writer records his experiences and observations while so employed.

We are inclined to feel, at times, that laboratory work will not be our concern as busy physicians. Consider this thought again. First, how many of us will have the immediate facilities of a first class laboratory when we start in practice? Perhaps 50%. The rest will have to rely largely on their own skill and accuracy in laboratory procedure for diagnosis. Also, consider the physician who cannot do the tests which he refers to the laboratory. He may not not recognize the occasional error; he may not appreciate the impossibility of completing tests within his time requirements; and he will be unable to appreciate or direct the finer points of technique which may often give the clue to a difficult diagnosis.

During July and August of 1946 I was an assistant x-ray and laboratory technician in a small Saskatchewan hospital of 126 beds. This laboratory is very well equipped and efficiently managed. I consider that my time was very well spent and the remuneration was quite adequate, a consideration for many students.

Procedure done in this laboratory were many. Most hemocytology work, including photo-electric colorimetery, icterus indices. dark-field examinations and blood chlorides, was carried out. Plate counts on local milk supplies were also done. Gastric analyses, sputum examinations, g.c. cultures and basal metabolism tests were amongst the many other procedures in which I was able to assist. However, I found that completion of the first medical year was not adequate training for all these procedures. The second year student would find himself much better qualified. Nevertheless I feel that in doing the simpler laboratory procedures such as urinalyses, to which lack of experience largely confined me, I derived considerable benefit. I had ample opportunity to do the more difficult tests on the various lab. specimens and to compare my results with those of the head technician. Good notes and texts were available for guidance.

I spent more time on Roentgenography than in the laboratory. After a few days of instruction and operation under observation it is possible to take and develop many of the routine X-rays. The finer points of X-ray technique take many years to acquire but they can be much better appreciated after actual experience in X-ray procedure. There was opportunity to study these X-ray plates and attempt a diagnosis which I could check with the doctor in charge of the case. The doctors were very helpful in discussing their plates and pointing out the lesions or pathology indicated in them. Of particular interest were the gastro-intestinal visualizations by barium meals and the urinary tract visulations by intravenous injections of a radio-opaque dye. Fractures and dislocations also were not infrequent, and often resulted in night calls for emergency X-ray plates.

Experience in Roentgenography gives one an appreciation of the finer points of technique, which, as in laboratory work, may make a difficult diagnosis much easier.

The doctor who understands those variations in X-ray procedure which will bring out the desired degrees of density, contrast and definition in his films can achieve a high degree of success in their interpretation.

Obtaining a laboratory position may be difficult. However there are many small hospitals in Ontario which may require an assistant laboratory or X-ray technician during the summer months. To those students who have the good fortune of obtaining such a position, I can give assurance, from my own experience, that they will have a satisfying vacation.

Abstracts

C. L. ASZKANAZY, Editor

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PUBLIC HEALTH I

DANGERS ASSOCIATED WITH USE OF LIVING "ATTENUATED" TYPHUS VACCINE. J. F. Sadusk Jr. and H. Kuhlenbeck: Amer. J. Pub. Health *36,* 1027 (1946).

AN account is given of the difficulties encountered by the Japanese health authorities following the administration of bilated living murine typhus vaccine. Seventy percent (218) of a group of two hundred ninety receiving inoculations of this vaccine developed symptoms and serologic manifestations of typhus fever. There was one fatality. The use of living typhus vaccine has resulted in a series of frank failures. Sadusk and Kuhlenbeck stress the favorable results which have been recently obtained against epidemic typhus fever by the use of a killed ether extracted yolk sac vaccine.

G. W. B. C.

MEDICINE I

PRELIMINARY OBSERVATIONS ON DIURNAL AND OTHER VARIATIONS IN HEMOGLOBIN LEVELS: W. Wilkins and Ruth Blakely, Milbank Memorial Fund Quarterly, *24,* 359-372 (1946).

THE morning and afternoon hemoglobin levels were determined on six hundred and fifty-one adults and children, for both capillary and venous blood samples. The data obtained showed considerable variation during the day and in the majority of cases lower values were obtained in the afternoon.

Hemoglobin levels were determined on a group of twenty-one college girls five times during the day between 7:00 A.M. and 10:00 P.M. For every subject, the highest values were obtained in the morning. In eighteen subjects, the lowest values were obtained between 2:00 and 5:00 P.M. In the remaining three, the lowest values were obtained in the venous but not capillary blood in the evening. In those subjects with low afternoon values, there was a significant tendancy for the hemoglobin values to rise in the evening.

G. W. B. C.

MEDICINE II

EVALUATION OF SEVERAL METHODS FOR TREATING GRAVE'S DISEASE AVAILABLE TODAY. J. H. Means: Ann. Internal Med. *25,* 403 (1946).

Means believes that patients with hyperthyroidism can be prepared more completely for thyroidectomy than heretofore by the use of antithyroid drugs such as thiouracil in combination with iodine. The author still favors thyroidectomy after preparation with an antithyroid drug in combination with iodine rather than prolonged treatment with an antithyroid drug alone. Radioactive iodine provides an effective way of producing a remission in the thyrotoxicosis of hyperthyroidism. Its final evaluation in comparison with other methods of treatment, however, must await further observation of more cases over a longer period of time. Possible untoward side-effects, malignancy and renal damage must be considered and further investigated.

G. W. B. C.

MEDICINE III

Intoxication Resulting From Administration of Massive Doses of Vitamin D, With Report of Five Cases. G. W. Covey and H. H. Whitlock: Ann. Internal Med. *25,* 508 (1946).

The authors state that vitamin D in massive doses is a powerful and dangerous drug which should be used with caution and that there are definite contraindications to its use. Calcium is mobilized from the bone trabeculae with consequent rise in the blood calcium level. Cellular degeneration is produced in various organs particularly the kidney. The degenerated cells become calcium repositories. Presumably because of the inability of the damaged kidney to excrete it, nitrogen often accumulates in the blood.

Mild intoxication with vitamin D, unless permitted to continue for a long time, is probably harmless and complete restitution of the injured tissues usually takes place.

Four of five patients, ranging from 29 to 68 years of age, took doses of 150,000 units per day, an amount larger than is considered safe. Two of the five patients had arteriosclerosis and hypertension, conditions which have been said to contraindicate the use of this drug. Two of the patients voluntarily increased the dosage beyond the amount ordered. The mental status of the first patient, though not obviously psychotic, deteriorated in comparison with previous observations. Especially in the aged, it is probable that psychic disorders should be considered as contraindications to the use of massive doses of vitamin D.

The most common symptoms were headache, nausea, and vomiting. These were associated with a group of findings indicating renal injury. The authors conclude that the use of this vitamin should always be very carefully supervised.

G. W. B. C.

MEDICINE IV

Pulmonary Tuberculosis in Harvard Medical Students. H. P. Brean and L. W. Kane: New England Jl. Med. *235,* 315 (1946).

The authors claim that pulmonary tuberculosis remains the most serious medical problem confronting the medical student. The records of the Harvard Med-

ical School health office regarding pulmonary tuberculosis during the past twenty-three years are reviewed. Significant active adult type pulmonary tuberculosis has an incidence rate of 2.2 percent. The number of cases discovered during the last two academic years was four times as great as the number developing during the first two years but the incidence of acquisition of tuberculous infection was about the same (12-13% annually) for each academic year.

That factors other than the opportunity for infection are responsible for the increase in cases during the period of clinical training is suggested by the constant annual attack rate. Duration of disability was closely related to the severity of the pulmonary lesion at the time it was discovered. Lesions detected by the appearance of symptoms were of greater severity and associated with a much longer period of disability than those discovered by routine methods. A program of surveys more frequent than once a year led to the elimination of nearly all symptom detected cases and of all major lesions. A semi-annual examination represents the maximum interval for routine re-examination by X-ray or tuberculin tests not only for medical students but also for nurses and interns.

W. G. B. C.

PAEDIATRICS I

Use of Gamma-globulin in Prophylaxis of Measles. S. G. Anderson and W. M. Ket: Med Jl. Australia *2*, 196 (1946).

One hundred and sixteen children, closely exposed to infection during an epidemic of measles in Melbourne, were given prophylactic doses of gamma-globulin. Approximately one-half of them received 0.1 cc. of gamma-globulin per pound body weight while most of the others received 0.025 cc. per pound body weight. Sixty-seven of the children did not develop measles, forty-six had a modified attack, and in three the course of the disease was apparently uninfluenced by the globulin. More than three-quarters of those receiving the larger dose did not develop measles whereas more than half of those receiving the smaller dose developed modified attacks without complications. The three in whom the disease was apparently uninfluenced received the smallest dose.

G. W. B. C.

SURGERY I

Lenosity H. and Graham A. P. "Carcinoma of the Penis" J. Urol. vol. 56 No. 4 Oct. 1946.

The authors review the clinical histories of 100 white and 39 Negro patients with carcinoma of the penis.

The average time between onset of the lesion and admission to hospital was 21 months, both in the white and coloured men. Circumcision performed early in infancy is a prophylactic measure against cancer of the penis. Circumcision later in life does not prevent its development.

The incidence of venereal disease in this group of patients was found to be considerably higher than in the general population.

Cutaneous cancer is seven times more common in the white population, but malignancy of the penis occurs 5½ times more frequently in the Negro.

Marriage has no influence on the development of this disease. Cancer of the penis made up approximately 1% of all the cancers in the male. It occurs most frequently in the 40-49 years age group, falling off with increasing age.

The papillary type is far more frequent than the ulcerating type. The site of origin in order of frequency is (1) frenum or prepuce, (2) glans, (3) corona. Inguinal metastases were present in one-third of the patients admitted. The cancer is of low-grade malignancy and may grow slowly for many years.

Predisposing causes are irritation, trauma, and chronic inflammatory processes.

For treatment, 53 patients were given radiation only. Of this group, 62% are alive after 5 years. The best results were obtained in men who had a lesion of 2 cm. or less in diameter and no involvement of the deeper fascia. Preoperative irradiation of metastatic nodes is ineffective in clinically arresting the disease. Preoperative irradiation of the penile lesion shrinks the tumour mass and prevents possible tumour cell dissemination. Post-operative irradiation after block dissection of the groin decreases the incidence of recurrences. Major surgery was performed on 82 patients of whom 57.3% are alive after 5 years. The scrotum and its contents are excised only if involved by the malignant growth.

W. B. W.

OBSTETRICS I

Nutrition in Pregnancy. The Effects of Dietary Deficiencies in Pregnancy and the Detection and Treatment of Nutritional Deficiency Diseases. C. F. Vilter, D. Morgan, Tom Spies: Am. Journal Obst. and Gynec. Vol. 83, No. 5, Nov. 1946.

The authors review our present-day knowledge of dietary deficiencies in pregnancy and their effective treatment. Clinical evidence of dietary deficiencies show commonly in the later half of pregnancy when the fetal demands are greatest. Mild nausea and vomiting of the first trimester of pregnancy and food idiosyncrasies may initiate faulty dietary habits for the rest of the term. Prophylaxis is by proper dietary education. The size of the family is directly proportional to the mother's nutritional status, signs of nutritive failure commoner in 6th or 7th than in 1st or 2nd pregnancy. This is based on a study on 229 pregnant women at the Nutrition Clinic in Birmingham, Alabama. Among the predisposing factors was found:

(1) Low family income,

(2) Hyperemesis Gravidarum giving rise to pellagra, scurvy, polyneuritis, nutritional anemia.

Studies of Brown, Ebbs, Tisdall on deficient and adequate diets during pregnancy showed fewer complications during pregnancy and delivery in mothers with adequate diets and higher morbidity and mortality in infants of mothers on poor diets. The deficit may only be preclinical or biochemical.

Isolated syndromes are always a manifestation of general deficiency.

An optimum diet during pregnancy should contain 3500-400 Cals., including 10-150 Gm. protein, adequate vitamins and minerals. If not enough vitamins in the diet, synthetic vitamins should be added. Specific therapy with synthetic vitamins must be given at prominent symptoms.

R. I.

RECENT ACCESSIONS TO THE MEDICAL READING ROOM

Albrecht, F. K.: Modern management in clinical medicine. 1946.
Alexander, F. and French, T. M.: Psychoanalytic therapy. 1946.
Aykroyd, W. R.: Nutrition. 1946.
Bancroft, F. W. & Humphreys, G. H. (eds.): Surgical treatment of the soft tissues. 1946.
(Banting, (Sir) Frederick Grant:) Harris, S.: Banting's miracle. 1946.
(Banting, (Sir) Frederick Grant:) Shaw, M. M.: He conquered death. 1946.
(Banting, (Sir) Frederick Grant:) Stevenson, L.: Sir Frederick Banting. 1946.
Beaumont, W.: Experiments and observations on the gastric juice and the physiology of digestion; facsimile of the original edition of 1833.....1941.
Berens, C. and Zuckerman, J.: Diagnostic examination of the eye. 1946.
Bicknell, F. and Prescott, F.: The vitamins in medicine. ed.2. 1946.
Bistran, W. J.: Physician's prescription manual. 1946.
Bonney, V.: The technical minutiae of extended myomectomy and ovarian cystectomy. 1946.
Braun-Menéndez, E. and others: Renal hypertension; tr. by Dexter. 1946.
Brill, A. A.: Lectures of psychoanalytic psychiatry. 1946.
Campbell, A. D. and Shannon, M. A.: Gynecology for nurses. 1946.
Campbell, J. D.: Everyday psychiatry. 1945.
Collens, W. S. and Boas, L. C.: The modern treatment of diabetes mellitus. 1946.
Committee on tuberculosis in industry: Industry, tuberculosis, silicosis and compensation. 1945.
Cornell conference on therapy. vol. 1. 1946.
Derbes, V. J. and Engelhardt, H. T.: The treatment of bronchial asthma. 1946.
Dobson, J.: Anatomical eponyms. 1946.
Everett, M.R.: Medical biochemistry, ed.2. 1946.
Fearon, W. R.: An introduction to biochemistry. ed.3. 1946.
Graybiel, A. and White, P. D.: Electrocardiography in practice. ed. 2. 1946.
Glueck, B. (ed.): Current therapies of personality disorders. 1946.
Gross, M.: Acetanilid. 1946.
Herz, E. and Putnam, T. J.: Motor disorders in nervous diseases. 1946.
Holmes, G.: Introduction to clinical neurology. 1946.
James, N. R.: Regional analgesia for intra-abdominal surgery. 1944.
Léger, L. and Olivier, C.: Entorses du cou-de-pied et entorses du genou. 1945.
Leithauser, D. J.: Early ambulation and related procedures in surgical management. 1946.
Luria, A. R.: Nature of human conflicts; tr. by Gantt. 1932.
New York Academy of Medicine: The march of medicine, (Modern attitudes in psychiatry) 1945.
Nielson, J. M.: Agnosia, apraxia, aphasia. 1946.
Preston, G. H.: Psychiatry for the curious. 1940.
Preston, G. H.: The substance of mental health. 1943.
Quigley, T. B.: Plaster of Paris technique in the treatment of fractures and other injuries. 1945.
Rank, O.: Will therapy and truth and reality. tr. by Taft. 1945.
Rufinus (13th cent.): The herbal of Rufinus, edited from the unique manuscript by L. Thorndike. 1946.
Schwab, G. M. (ed.): Handbuch der Katalyse. vol. 3. Biokatalyse. 1941.
Scott, W. A. and Van Wyck, H. B.: The essentials of obstetrics and gynecology. 1946.

Selye, H.: Encyclopedia of endocrinology. Section 4, the ovary; vol. 4.—Ovarian tumors. 1 vol text, 1 vol. bibliography. 1946.
Semon, H. C. G.: An atlas of the commoner skin diseases. ed. 3. 1946.
Soffer, L. J.: Diseases of the adrenals. 1946.
Sorsby, A.: Ophthalmia neonatorium. 1945.
Stevansson, V.: Not by bread alone. 1946.
Stutterheim, N. A.: Squint and convergence. 1946.
Tiegs, E. W. and Katz, B.: Mental hygiene in education. 1946.
Travel, F. von: Die Auswirkungen des sauer stoffmangels auf den menschlichen Organismus bei Kurzfristigen Aufenthault in grosser Höhe. 1943.
Thorek, M.: The face in health and disease. 1946.
Vitamins and hormones. vol. 4. 1946.
U.S. Strategic Bombing Survey, Morale Division: The effect of bombing on health and medical care in Germany. 1945.
Verzar, F.: Höhenklima-Forschungen des Basler Physiologischen Institutes. 1945.
Vischer, A. L.: Das Alter als Schicksal und Erfüllung ed. 2, 1945.
Wright, S.: Applied physiology, ed. 8, 1946.

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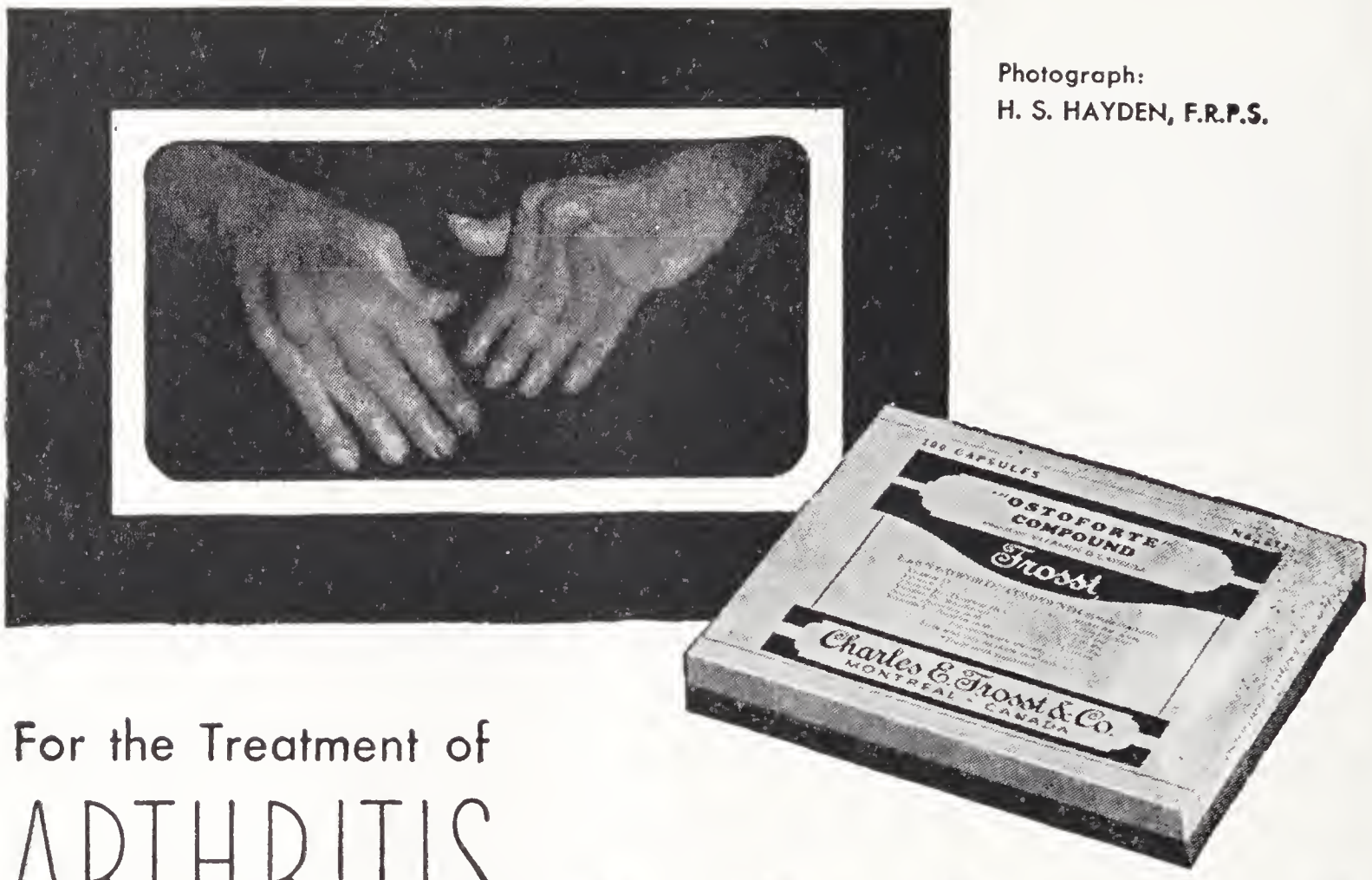

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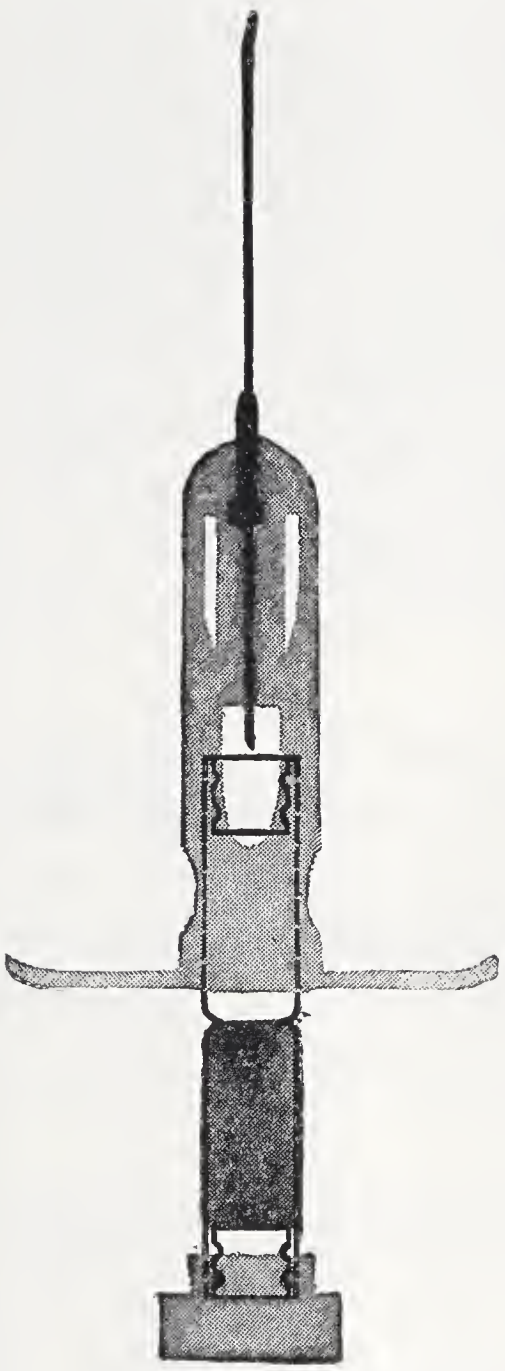

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1. Kirby, W. M. M.; Leifer, W.; Martin, S. P.; Rammelkamp, C. H., and Kinsman, J. M.: J.A.M.A. 129:940 (Dec. 1) 1945.
2. Nichols, D. R., and Haunz, E. A.: Proc. Staff Meet. Mayo Clinic 20:403 (Oct. 31) 1945.
3. Romansky, M. J., and Rittman, G. E.: New England J. Med. 233:577 (Nov. 15) 1945.

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*R. H. Follis, D. Jackson, M. M. Eliot, and E. A. Park: Prevalence of rickets in children between two and fourteen years of age, Am. J. Dis. Child. 66:1-11, July 1943.

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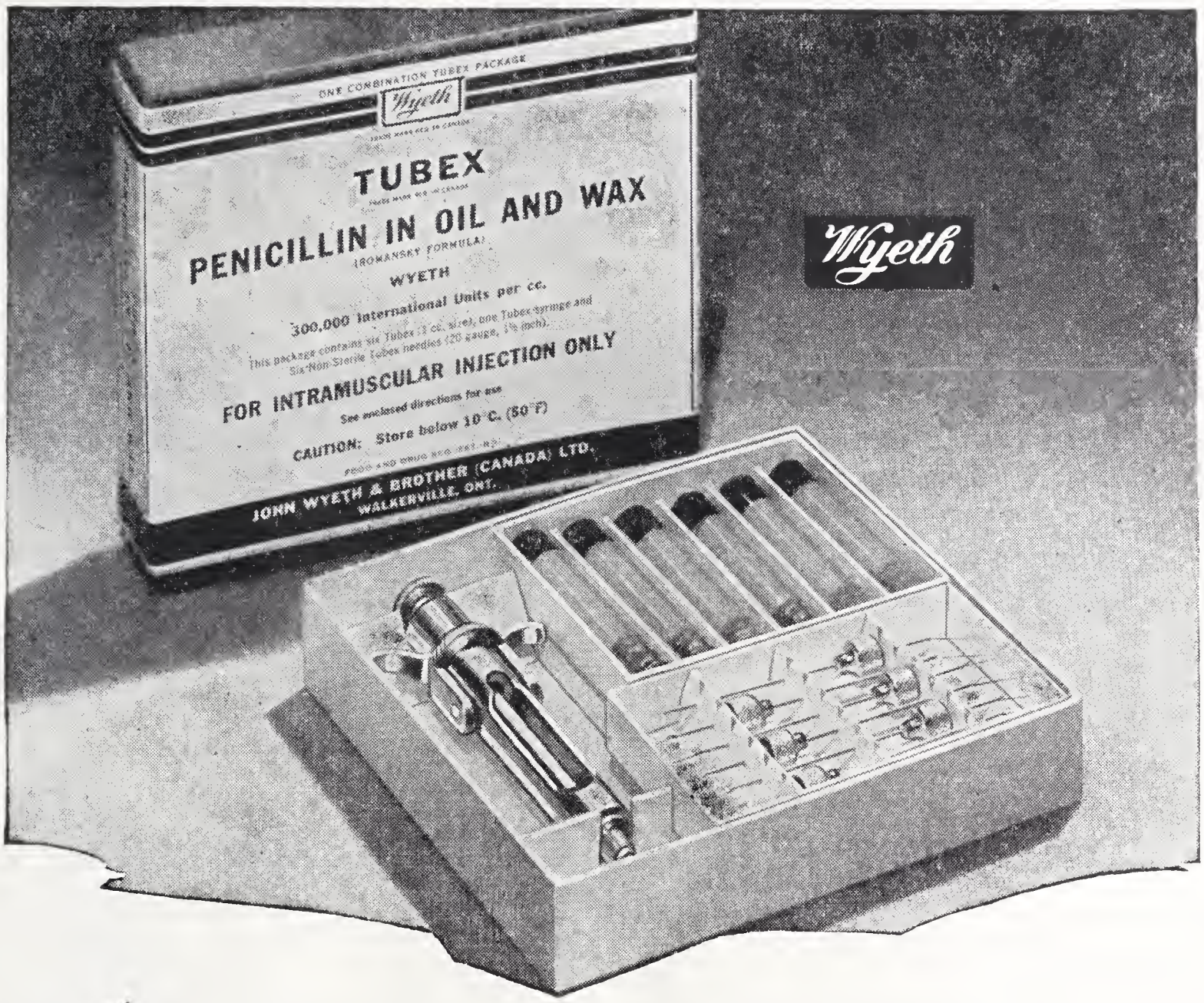
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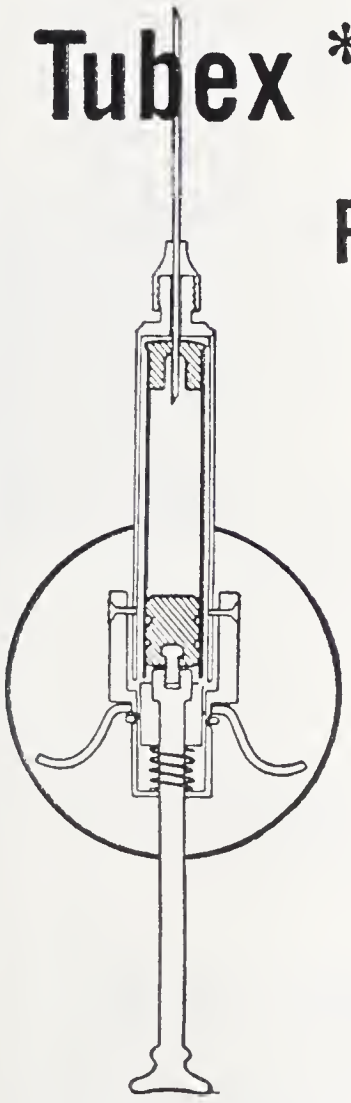

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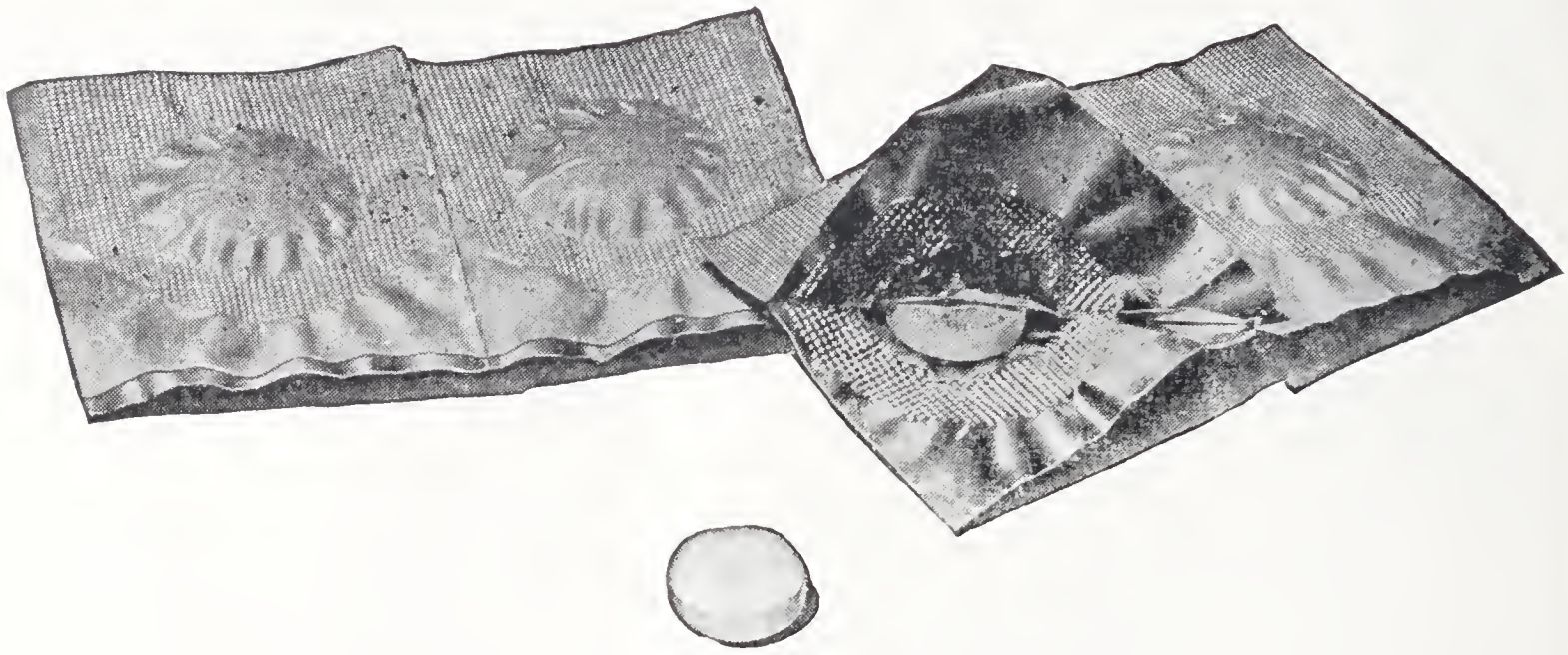

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1. Bunn, P. A.: in Conferences on Therapy: New York State J. Med. 46:527 (March 1) 1946.
2. György, P.; Evans, K. W.; Rose, E. K.; Perlingiero, J. G., and Elias, W. F.: Pennsylvania M. J. 49:409 (Jan.) 1946.

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